MODERN DERMATOLOGIC THERAPY

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MODERN DERMATOLOGIC THERAPY

EDITED BY

THOMAS H STERNBERG M D

Professor of Medicine (Dermatology) and
Assistant Dean for Postgraduate Medical Education
University of California (Los Angeles) School of Medicine

VICTOR D NEWCOMER M D

Associate Professor of Medicine (Dermatology)
University of California (Los Angeles) School of Medicine

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CONTRIBUTORS

SAMUEL AYRES JR., M.D Clinical Professor of Medicine (Dermatology) University of California (Los Angeles) School of Medicine

RUDOLF L. BAER, M.D Professor of Clinical Dermatology and Syphilology New York University Postgraduate Medical School, Associate Director Skin and Cancer Unit, and Attending Dermatologist, New York University Hospital.

G DOUGLAS BALDRIDGE, M.D Assistant Clinical Professor of Medicine (Dermatology and Syphilology) University of Southern California School of Medicine.

S. WILLIAM BECKER, M.S M D Clinical Professor of Medicine (Dermatology and Syphilology) University of Southern California School of Medicine

NORMAN Q BRILL, M.D Professor and Chairman of the Department of Psychiatry University of California (Los Angeles) School of Medicine.

FLOYD M ESTESS M.D Assistant Professor of Psychiatry University of California (Los Angeles) School of Medicine.

CARLYN HALDE, Ph.D Assistant Research Microbiologist, Department of Medicine, Division of Dermatology University of California (Los Angeles) School of Medicine.

JOHN A. HOSMER, M.D Clinical Instructor in Medicine (Dermatology) University of California (Los Angeles) School of Medicine.

EDWARD L. LADEN M.D Assistant Clinical Professor of Medicine (Dermatology) University of California (Los Angeles) School of Medicine.

PAUL LEVAN, M.D. Assistant Clinical Professor of Medicine (Dermatology), University of California (Los Angeles) School of Medicine

MORGAN C. LINDBERG, M.D. Fellow in Dermatology, Department of Medicine, Division of Dermatology, University of California (Los Angeles) School of Medicine.

VICTOR D. NEWCOMER, M.D. Associate Professor of Medicine (Dermatology), University of California (Los Angeles) School of Medicine

CARL PEARSON, M.D. Assistant Professor of Medicine in Residence, University of California (Los Angeles) School of Medicine

DANIEL J. PERRY, M.D. Associate Clinical Professor of Medicine (Dermatology), University of California (Los Angeles) School of Medicine

WILLIAM N. PIPER, M.D. Assistant Clinical Professor of Medicine *(Dermatology), University of California (Los Angeles) School of Medicine*

HAROLD PRICE, M.D. Assistant Clinical Professor of Medicine (Dermatology), University of California (Los Angeles) School of Medicine

RONALD M. REISNER, M.D. Assistant Resident in Medicine (Dermatology), University of California (Los Angeles) School of Medicine

WALTER B. SHELLEY, M.D., Ph.D. Professor of Dermatology, University of Pennsylvania Medical School.

THOMAS H. STERNBERG, M.D. Professor of Medicine (Dermatology) and Assistant Dean, University of California (Los Angeles) School of Medicine.

FRANK F. TALLMAN, M.D. Professor of Psychiatry, University of California (Los Angeles) School of Medicine

EDWIN T. WRIGHT, M.D. Assistant Clinical Professor of Medicine (Dermatology), University of California (Los Angeles) School of Medicine, Veterans Administration Center, Los Angeles.

ROBERT H. ZEILENGA, M.D. Clinical Instructor in Medicine (Dermatology), University of California (Los Angeles) School of Medicine, Veterans Administration Center, Los Angeles.

During recent years the tendency in didactic postgraduate teaching has been toward the two- or three-day seminar or conference with panel-type discussions and presentations. At these meetings, different aspects of a selected subject are presented and new information and thought in relation to diagnosis and treatment are emphasized.

Here at the U.C.L.A. Medical Center a large number of such conferences have been sponsored by the Division of Postgraduate Medical Education and have become quite popular with the practitioner students. At many of the conferences, invited national authorities participate in the presentations. Early in the program it was noted that the students constantly requested a summary of the proceedings so that they might have take home material which could be referred to at a later date. In response to these requests, Medical Extension initiated a policy of having a syllabus prepared to be given to the students at the time of the meeting or shortly thereafter Since the compilation of these papers represented an up-to-date volume on the subject which was presented, it occurred to us that because reference volumes lagged behind actual research productivity many of these syllabi would be in demand if they were available as a published book.

At about this time, the Blakiston Division of the McGraw Hill Book Company suggested the possibility of developing a series of short practical volumes based on these conferences or symposia, thus making available the latest collective thinking on topics of current importance. After considerable discussion and review President Robert G Sproul approved this plan and a committee was appointed in the Medical Center to assist in the

selection of the subjects and the publication of the volumes under the general title University of California Medical Extension Series, Los Angeles. The committee is composed of myself as Chairman, with Dr Morton H Maxwell representing the Department of Medicine and Dr Franklin L. Ashley representing the Department of Surgery

"The Differential Diagnosis of Abdominal Pain," edited by Dr Sherman Mellinkoff and the present volume Modern Dermatologic Therapy are the first two volumes to be published under the agreement between McGraw Hill and the Division of Postgraduate Medical Education, University of California Medical Center Los Angeles. It is planned that four to six volumes will be published yearly Those now in preparation cover such topics as sterility disorders of fluid and electrolyte metabolism peripheral vascular disease and emotional problems. It is our intention to continue selecting such topics of current interest and importance

Thomas H Sternberg, M D
Professor of Medicine (Dermatology) and
Assistant Dean for Postgraduate
Medical Education

PREFACE

Significant and rapid advances in many areas of dermatology and closely allied fields have been made in recent years and have necessitated alterations in the therapy of many of the commonly encountered dermatologic conditions.

This tremendous surge of investigative endeavor at both a clinical and a basic level has produced an overwhelming volume of data requiring newer types of approaches, directed toward assimilation evaluation, and dissemination. One such popular approach has been the development of the postgraduate symposium, a serious drawback of which, however is the limited number of people to whom it is available. There has been, therefore, in recent years an increasing trend toward widening the potential value of such symposia by publishing their proceedings.

Accordingly a 2-day symposium, sponsored by the Division of Dermatology and offered through the Division of Postgraduate Medical Education, School of Medicine, University of California at Los Angeles, was held for the purpose of presenting recent research developments in dermatology with special emphasis directed toward their influence on currently accepted methods of treatment. It will be noted that there are several large areas deserving coverage that have been omitted. This was not an oversight but rather was necessitated by the limitations of both the symposium and publication.

The success of this symposium was in large part due to the planning and hard work of the staff of the Division of Postgraduate Medical Education of the School of Medicine, University of California at Los Angeles: Mrs. Bettie Minifie, Mrs.

selection of the subjects and the publication of the volumes under the general title, "University of California Medical Extension Series, Los Angeles." The committee is composed of myself as Chairman, with Dr. Morton H. Maxwell representing the Department of Medicine and Dr. Franklin L. Ashley representing the Department of Surgery.

"The Differential Diagnosis of Abdominal Pain," edited by Dr. Sherman Mellinkoff and the present volume "Modern Dermatologic Therapy" are the first two volumes to be published under the agreement between McGraw-Hill and the Division of Postgraduate Medical Education, University of California Medical Center, Los Angeles. It is planned that four to six volumes will be published yearly. Those now in preparation cover such topics as sterility, disorders of fluid and electrolyte metabolism, peripheral vascular disease, and emotional problems. It is our intention to continue selecting such topics of current interest and importance.

Thomas H. Sternberg, M.D.
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Assistant Dean for Postgraduate
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ODERN DERMATOLOGIC THERAPY

Victor D. Newcomer
and Ronald M. Reisner

MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) was considered until recently to be a rapidly progressive disease occurring predominantly in young women and pursuing an invariably fatal course within a 2 year period. The discovery of the LE cell phenomenon by Hargraves, Richmond, and Morton [1] in 1948 not only stimulated the widespread study of this phenomenon itself but also provided a test which, because of its high degree of specificity has been of great value in elucidating the natural history and protean manifestations of this disease.

SLE is now known to occur with a much greater frequency than was formerly suspected [1–5] presenting itself in a wide variety of dissimilar clinical pictures. The disease may vary in severity from a mild, self-limited syndrome through all intermediate stages to the previously recognized rapidly fatal fulminating form. Spontaneous exacerbations and remissions occur the latter lasting at times for a period of years. All ages and races, and both sexes, may be involved.

Advances in other fields have also had a direct bearing on a better understanding of SLE. For example, Rein and Kostant [6]

in 1950 pointed out the high percentage of biological false-positive reactions in patients with lupus erythematosus and stated that such serologic phenomena may be the first and *only sign of LE and may warn of impending clinical activity.* Haserick and Long [7] in 1952 reported for the first time a series of five cases in which discovery of the biological false-positive reaction preceded the clinical manifestations of LE for from 1 to 7 years, and suggested that in some cases the biological false-positive reaction may be the first indication of LE. They emphasized the importance of further evaluation of the chronic biological false-positive reactor for possible latent LE, particularly in the presence of a typical rheumatoid arthritis, rheumatic fever and glomerulonephritis, and stressed the use of the LE cell test in evaluating such cases.

In 1949 Nelson and Mayer [8] described the *Treponema pallidum* immobilization (TPI) test, which later studies have demonstrated to be highly specific for syphilis and related treponematoses. Moore and Mohr [9, 10] utilizing the high specificity of this test, investigated the incidence and causes of biological false-positive reactions to serological tests for syphilis and concluded that the chronic biological false-positive reaction is far from innocuous and may be the first evidence of serious underlying disease, and further that collagen disease may be closely related to the chronic biological false-positive reaction, which may provide an opportunity to define more clearly the natural history and early manifestations of the collagen diseases. Moore et al. [3, 4] then attempted to study the natural history of LE by studying patients with chronic biological false-positive reactions for syphilis, and concluded (1) that collagen vascular disease especially SLE, is not rare but instead is much more common than was heretofore recognized (2) that SLE is neither necessarily nor even often acute or subacute but instead may be exceedingly chronic lasting for many years or even decades (3) that the clinical course of SLE is often relatively benign (4) that SLE is not uniformly fatal.

On the basis of these more specific tests many previously unrecognized atypical forms of SLE have been described. Russell

et al. [11] have emphasized the neurological manifestations of SLE and have suggested that epilepsy when accompanied by rheumatoid arthritis or leukopenia, may constitute a prodromal symptom of LE.

SLE may also appear initially as a hematological disorder and acquired hemolytic anemia and thrombocytopenic purpura have recently been emphasized as presenting manifestations [12, 13] Recently Ward and Gunther [5] have suggested that toxemia of pregnancy may in some instances be a manifestation of SLE. Shipton, in the discussion of this paper agreed and underlined its possibility as a cause in those cases with an associated psychosis.

Finally an old controversy namely the relationship between discoid LE and SLE, has become the subject of renewed interest. Several investigators have recently published studies [14–21] suggesting that discoid LE and SLE are phases of the same basic disease entity and that approximately 20 to 25 per cent of subacute and acute SLE is preceded by chronic discoid LE. All stressed the need for a thorough study of patients with discoid LE and careful observation for possible development of the acute or subacute systemic phase of the disease.

To cover SLE in all its various facets is beyond the scope of this paper The interested reader is referred to several recent comprehensive monographs [21–23] and review articles [24–29, 96]

The treatment of discoid LE will not be discussed, as it will be presented in detail elsewhere in this symposium [30]

THERAPY

Practically every therapeutic agent and approach which has become available in medicine has been used at one time or an other in the treatment of LE. These have included the use of bismuth, arsenic, phosphorous, gold, potassium iodide, quinine, para-aminobenzoic acid, salicylates, ergotin, digitalis, belladonna, iodide of starch, salicin, thyroid, testosterone, estrogen, adrenocortical steroids, ACTH thyroidectomy splenectomy oophorectomy heliotherapy vitamin B $_{12}$, antimalarials, nitrogen mustard,

in 1950 pointed out the high percentage of biological false-positive reactions in patients with lupus erythematosus and stated that such serologic phenomena may be the first and only sign of LE and may warn of impending clinical activity Haserick and Long [7] in 1952 reported for the first time a series of five cases in which discovery of the biological false-positive reaction preceded the clinical manifestations of LE for from 1 to 7 years, and suggested that in some cases the biological false-positive reaction may be the first indication of LE. They emphasized the importance of further evaluation of the chronic biological false-positive reactor for possible latent LE, particularly in the presence of a typical rheumatoid arthritis, rheumatic fever and glomerulonephritis, and stressed the use of the LE cell test in evaluating such cases.

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On the basis of these more specific tests many previously unrecognized atypical forms of SLE have been described Russell

the patient will not appear to be ill enough at the time of the initial examination, nor his symptoms sufficiently incapacitating, to reflect the serious nature of the underlying disease process. It is in this group of patients that such triggering factors as drug allergy sun exposure, intercurrent infection, trauma, overexertion, and emotional upset may precipitate an acute crisis. Therefore, it is our feeling that wherever possible patients exhibiting non specific constitutional symptoms such as fever generalized ma laise, weakness, arthralgias and arthritis, fleeting dermatitides, weight loss, and anorexia should be placed at bed rest and preferably hospitalized *until a thorough evaluation of their status* can be completed. In those patients where light sensitivity is thought to play a major causative role it has been recommended that the patient, in acute cases, be kept in total darkness for days or weeks, or that the windows be covered with red cellophane for the purpose of tiding the patient over an acute light-exacerba tive tendency [32, 33] However this is seldom done today The decision as to when to release the patient from bed rest is pri marily one based on a consideration of the individual total clinical picture, but certain general observations can be made. Bed rest is desirable as long as general symptoms indicate ac centuated activity or progression of the disease process, particu larly in those instances in which major organs are involved. The persistence of minor clinical and laboratory abnormalities, how ever does not in itself necessitate continued bed rest in a patient in whom the disease has otherwise shown evidence of having stabilized and after the patient has approached return to his normal weight, strength, and sense of well-being. Return to nor mal activity should be gradual over a period of at least several weeks, with adequate consideration of the limitations imposed by the knowledge that the disease may be exacerbated by a wide variety of stresses including infection, trauma, overexertion, and exposure to sunlight.

Diet. It is well recognized that good nutrition is essential for the patient who has active SLE. However it should be empha sized that good nutrition is equally important in the patient in total or partial remission to promote maximum health.

vitamin E, various antibiotics, small whole blood transfusions, concentrated white blood cell transfusions and triethylene melamine. None of these has proved consistently valuable in the management of this disease with the exception of the adrenocorticosteroids and ACTH which at present are the mainstays in the treatment of SLE.

Many of the drugs to which value has been attributed in the past are now known to be of little or no use and attest to the difficulty of evaluating therapeutic agents in a disease such as LE. The occurrence of spontaneous remissions in from 20 to 40 per cent of cases, the obscurity of exact time of onset [27] the variable classifications used in the different medical specialties [26] the small size of most series, the wide spectrum of severity *with which the disease may manifest itself its chronicity in some* cases, as well as the difficulty of setting up a control study because of the clinician's reluctance to withhold any potentially effective medication in so serious a disease [31] all combine to make evaluation of any therapeutic regimen extremely difficult and to explain some of the differences of opinion regarding management of SLE. There is no specific cure currently available for SLE however there are several valuable therapeutic modalities upon which the vast majority of clinicians agree These should be differentiated from experimental sojourns into the field of therapeutics for the purpose of improving current standards in the treatment of the disease This paper deals primarily with the currently accepted methods employed in the treatment of SLE.

General Methods

Bed Rest Probably the oldest and one of the most valuable supportive measures is that of bed rest [21–23] Historically it is well known that complete physical and mental rest are conducive to the initiation of a spontaneous remission, and bed rest is certainly essential in the management of acute SLE. Because of the numerous symptoms that the physician may be confronted with, the question may arise as to what criteria dictate the need for bed rest. There is no question concerning the need for bed rest in those patients who are overtly ill. However in many instances

STEROID THERAPY

General Considerations

Prior to the advent of the adrenocorticosteroids a large number of medicaments had been used in the treatment of SLE with only sporadic and indifferent results. In April, 1949, Hench and his coworkers presented their dramatic findings in respect to the use of 17-hydroxy-11-dehydrocorticosterone (compound E, or cortisone) and pituitary adrenocorticotropic hormone (ACTH) in the treatment of rheumatoid arthritis [41]. As these materials became more widely available, reports appeared in the literature attesting their favorable influence on the course of acute SLE and other collagen diseases [42–46]. However, from the first it was recognized that these agents were suppressive, not curative. Despite this they are considered lifesaving in acute crises. Subsequent studies have dealt with larger series over longer periods of time, and more detailed consideration has been given to the value of these steroids in the treatment of various facets of this disease. Newer derivatives of these steroids have been investigated in the light of a better understood and changing concept of the natural history of SLE. Early investigators all agreed that these compounds (ACTH and cortisone) were valuable agents in the treatment of the acute SLE crisis and in many instances were lifesaving [45, 47–52]. All also agreed that the benefit was one of temporary remission. This was based on the observation that many of the underlying clinical and laboratory abnormalities such as the positive reaction to LE cell test, elevated erythrocyte sedimentation rate, anemia, and abnormal urinary findings, would persist in spite of clinical improvement. Further, it was often noted that withdrawal of steroids was followed shortly by recurrence and sometimes progression of the disease process. Because of this the question arose as to whether the use of these steroids actually prolonged the life expectancy of these patients. Dubois et al. in 1952 could find no evidence that the use of steroids actually prolonged the life expectancy of patients with SLE [53]. However, Haserick, in discussing the effect of the

steroids on the prognosis of SLE, felt that they had a dramatic and often lifesaving effect on the severe fulminating course of SLE, and that lengthening of life through the use of continuous uninterrupted maintenance therapy was accomplished [54]. In addition he stressed the great improvement in morbidity which statistics often fail to reveal. Dubois [55] recently has presented data from which he concludes that the lives of patients are prolonged significantly by steroid therapy. Finally, it can be stated that steroids still represent the mainstay of treatment of SLE.

Preparations Available

At present the following steroids have been found useful in the management of SLE: pituitary adrenocorticotropic hormone (ACTH), 11-dehydro-17-hydroxycorticosterone (cortisone), 17-hydroxycorticosterone (hydrocortisone), $\Delta^{1,4}$-pregnadiene-17α,21-diol-3,11,20-trione (prednisone) and $\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-20-dione (prednisolone), methylprednisolone, and 9α-fluoro-16α-hydroxyhydrocortisone diacetate (triamcinolone).

All these drugs, if given in their respective proper dosages, appear to be equally effective in the management of this disease. Table 1.1 shows the effective dosage for each.

Table 1.1 RELATIVE EFFECTIVE DOSAGES OF THE STEROIDS IN THE TREATMENT OF SLE

	Dubois [58]	Shulman [23] usual initial dose	Sternberg [57] usual initial dose	T Rott [22] usual initial dose	Dosage recommended in mg
ACTH				1 unit	
Cortisone	5	5	5 5		
Hydrocortisone	4	4	$\frac{2}{3}$–4	1 mg	
Prednisone	1	1	1		1
Prednisolone	1				1
Triamcinolone					$\frac{2}{3}$
Methylprednisolone					

Some of the advantages and disadvantages which have been attributed to these compounds are tabulated below

ACTH

1. Advantages
   a. Induces a more rapid remission in the acute lupus crisis [51 58]
   b. May prevent adrenal atrophy in the fetus in steroid treatment during gestation.
   c. Slower onset and lesser severity of relapses [59]
   d. More physiological stimulus.
2. Disadvantages
   a. Must be given parenterally
   b. Greater *mineralocorticoid* activity [53]
   c. Tendency to promote hypertension [53].
   d. Occasional allergic reactions because of protein nature.
   e. Greater incidence of hirsutism with long-term treatment.

Cortisone

1. Advantages
   a. May be taken orally
   b. Intermediate between prednisone and ACTH with regard to hypertension producing effects stemming from sodium retention.
   c. Less diabetogenic effect than prednisone [56]
   d. Less ulcerogenic effect than prednisone [56]
   e. Less tendency to produce ecchymotic skin lesions [56]
2. Disadvantages
   a. High rate of sodium and water retention relative to prednisone [56, 57]
   b. High rate of potassium loss relative to prednisone [56, 57]
   c. Greater tendency to produce Cushingoid state in therapeutic dosages than prednisone [56, 57]

Hydrocortisone

1. Advantage A preparation suitable for intravenous administration is available for use particularly in acute crises.
2. Otherwise the advantages and disadvantages are essentially the same as those of cortisone.

Prednisone:

1. Advantages
   a. Slower rate of sodium and water retention in therapeutic dosages.

b Slower rate of potassium loss in therapeutic dosages.
c. More effective on a mg per mg weight basis than cortisone or hydrocortisone [56, 57]
d. Less tendency to develop elevated blood pressure on therapeutic dosages.
e Less tendency to develop a Cushingoid state on therapeutic dosages [57].

2. Disadvantages
a Increased ulcerogenic tendency [56].
b Increased diabetogenic tendency [56]
c Increased incidence of ecchymotic skin lesions [56]

Prednisolone

1 Advantages are the same as those of prednisone
2. Disadvantage It is not as potent or dependable an antiinflammatory agent as prednisone [56].

Methylprednisolone

1 Advantages
a. No sodium or water retention [60]
b No potassium loss.
c Less disturbance of psychic equilibrium.
d Less incidence of peptic ulcer
e Less incidence of osteoporosis.
f Lower dosage levels required [60]

2. Disadvantage There is a narrower margin of safety between therapeutic and toxic doses.

Triamcinolone

1 Advantages
a. No sodium and water retention [61]
b No potassium loss [61]
c Less disturbance of psychic equilibrium.
d Low incidence of peptic ulcer
e Low incidence of osteoporosis.
f Lower dosage levels required [61]
g To date appears to exert a unique antiinflammatory effect on the skin.

2. Disadvantages are the same as those of methylprednisolone

Many of these advantages and disadvantages have with additional experience been demonstrated to be invalid. With proper dosage it is now well recognized that cortisone hydrocortisone and prednisone can each produce a clinical remission as rapidly

and as effectively as ACTH, and in fact may produce an even more rapid clinical response in comparable doses [59] Others feel that the newer steroids represent the current drugs of choice in the treatment of SLE and that ACTH has little place in the therapy of a chronic disease [55] Early in the use of the steroids in the treatment of SLE it was thought that it was necessary to produce a Cushingoid state to ensure maximal suppression of the disease process [53, 62] With the advent of the newer steroids, with their more potent antiinflammatory effect, it is generally agreed that routine induction of the overt Cushingoid state early in the treatment is no longer necessary for maximal suppression of the disease [21 22, 58] On the other hand, however some workers feel that although prednisone and prednisolone have definitely less sodium retaining potassium excreting tendencies, they may be more strongly diabetogenic and ulcerogenic [58]

Recently two new steroids, methylprednisolone and triamcinolone, have been introduced for clinical use on the basis that they possess even fewer of the side effects associated with all previous corticosteroids [60, 61] These include (1) no sodium or water retention, (2) no potassium loss, (3) no interference with psychic equilibrium, (4) low incidence of peptic ulcer and (5) low incidence of osteoporosis.

These have not been in use for a sufficient length of time to accumulate adequate experience to assign exact therapeutic val ues or to substantiate fully the claims made for these drugs. The authors preliminary experience with these drugs indicates that they are effective agents for the control of the symptoms of SLE but that they also do produce all the serious side effects which have previously been encountered with the use of the other corti costeroids. These include sodium retention, peptic ulceration in cluding perforating ulcers, osteoporosis, fractures, and disturbances of psychic equilibrium. Some of these effects have occurred while the patient has been receiving comparatively small doses of the drug.

In anticipation of the future development of multiple new and more potent antiinflammatory agents it is suggested that the physician familiarize himself thoroughly with one or two of these

preparations to the point of mastering their therapeutic abilities and shortcomings. This is in preference to immediate adoption of each new agent as it is introduced prior to adequate demonstration of the definite advantage of the newer agent over those previously employed.

Indications for Treatment

SLE varies in its manifestations through all degrees of severity and, in addition, the initial manifestations may involve any organ to any degree. Because of this the decision as to when to use the steroids remains one of individual clinical judgment in which the total clinical picture and the laboratory findings must be taken into account. No rigid criteria can be set up as to the indications for steroid therapy. However, it is generally recognized that the severely and acutely ill patient with SLE warrants immediate and effective steroid therapy. In this group are placed those patients presenting themselves with the so-called acute LE crisis, which is characterized by extreme prostration and fever together with manifestations of accentuated multiple system involvement. In such patients symptoms often appear in rapid succession, with death occurring early unless treatment is vigorous and prompt. It is in this group that the steroids have their most dramatic effect.

The early use of steroids is also recommended in those patients in whom it is demonstrated that there is early progressive involvement of certain vital organs including the lungs, heart, central nervous system, and hematopoietic system. This is particularly true in those instances where renal involvement is demonstrated, as it is now well accepted that extensive renal involvement is often irreversible and may be the major cause of death in some cases. Further, it has been shown that in some cases early renal changes are reversible with steroid therapy [55, 56, 63]. The use of steroids is also recommended in those patients whose disease may be of only moderate severity but in whom progression occurs in spite of an adequate trial of conservative treatment, including bed rest, salicylates, and, in selected cases, antimalarials. SLE undergoes spontaneous remission in 20 to 40 per cent of the cases.

therefore, in the milder cases of SLE in which there is not rapid progression or advanced specific organ involvement, most authorities agree that a trial of conservative treatment is indicated for the purpose of inducing such a spontaneous remission. This regimen includes bed rest, good nutrition, salicylates (particularly in cases with rheumatoid like arthralgias and arthritis) and in selected cases with predominantly cutaneous involvement a trial with *antimalarials*.

Dosage Schedules

The exact dosage to which the individual patient with acute SLE will respond varies from case to case, and in general the initial dose is arbitrarily chosen. Table 1-2 lists initial dosage schedules utilized by several investigators.

Table 1-2 SUGGESTED INITIAL DOSAGE SCHEDULES

	Shulman et al. [23]	Harvey et al. [21]	Steinberg et al. [57]	Dubois [53]	Talbott [22]	Authors experience
ACTH gel, units per day	60	40–60		40–80	40–80	
Cortisone, mg per day	800	200–300	100	300		300
Hydrocortisone, mg per day	240		80	240	40–80	240
Prednisone mg per day	60		20–30	40	10–20	60
Methylprednisolone, mg per day						48
Triamcinolone mg per day						48

Following the initial dosage further adjustment of daily dosage is determined by the clinical response of the patient. The earliest manifestations of adequate therapy are those of defervescence, improved feeling of well-being, improved strength, amelioration of arthralgias, and subsidence of signs of toxicity [21 48, 49, 51, 58, 64]

If however the steroid in the dosage used fails to produce such improvement within a period of 24 to 48 hours, an increase in the dosage is indicated. Increases may be of the order of magnitude of 25 to 100 per cent depending upon the urgency of the clinical picture [56] In some instances it has been necessary to employ dosages of cortisone (or its equivalent) as high as 2,000 to 3,500 mg per day to control patients in an acute crisis of SLE [56, 59] The majority of patients will respond at some dosage level. What ever this level proves to be, it should then be maintained wher ever possible until maximum improvement has been obtained. The majority of the significant symptomatology will be reversed on this regimen within 1 to 3 weeks in most patients [21] Once this state is achieved, the steroid dosage should be reduced in a stepwise fashion to the minimum level necessary to control the symptomatology adequately This required dosage for maintenance will vary from patient to patient and must be ascertained by careful individual adjustment. When large doses are employed initially the stepwise reduction may be in larger decrements at more frequent intervals, and as lower dosage levels are reached (in the realm of 10 to 40 mg of prednisone per day or its equivalent) decrements in the dosage should be of the order of 2.5 to 5 mg of prednisone or its equivalent at intervals of from 5 to 10 days in the average case. Frequently during the stepwise reduction of steroid dosage some of the former symptoms recur The dosage should then be maintained at this level, rather than immediately increased, until it is determined whether or not these symptoms constitute a temporary rebound phenomenon, in which case they will again subside without an increase in dosage. If such symptoms persist or progress them it may be assumed that additional steroid will be necessary to suppress the disease process. Once the minimal steroid dose needed to control clinical evidence of the disease adequately has been established, it should be maintained for at least several months before further efforts at dose reduction are undertaken. Infrequent attempts to discontinue the corticosteroids completely should be made, but complete withdrawal may not be possible.

Several methods of steroid administration have been em-

ployed on theoretical grounds with the purpose of attempting to prevent adrenocortical atrophy These methods have included

1. Intermittent cortisone therapy
2. Cortisone therapy alternating with ACTH therapy
3. Cortisone therapy with ACTH administered simultaneously

Accumulated experience indicates that permanent total adrenal atrophy rarely if ever occurs with prolonged adrenal steroid therapy [55] and that such schedules devised primarily to prevent this occurrence are not necessary and may complicate the management of the SLE itself Forsham [65] has recently stressed three types of dosage schedules—the replacement, maintenance, and suppressive schedules—and has emphasized that the clinical response constitutes the sole criterion of adequate dosage. He feels that maintenance dosage should be attempted in all but the most acute and life-threatening conditions "from the bottom up and suggests that one should attempt to give up to 30 mg of hydrocortisone or its equivalent at 9 A.M. This suggested approach in steroid therapy is based on the fact that normally the human adrenal cortex operates in a cyclic fashion producing about 70 per cent of its total daily output from 2 A.M. to 6 A.M. and that the administration of the above mentioned dosage of hydrocortisone at 9 A.M. circumvents the inhibition of pituitary ACTH production during the crucial night period, thereby making the drug additive. If such a regimen is unsuccessful, however the drug may be given every 6 hours, with an attempt to keep the total dose in the range of 30 to 60 mg of hydrocortisone (or its equivalent) a day Two methods are suggested for reducing the severity of transitory adrenal cortical insufficiency resulting from complete cessation of steroid therapy The first is that of slow reduction of total dosage of steroids ending by giving corticosteroids once a day at 9 A.M. for a period of 10 days for the purpose of allowing the pituitary adrenal system to return to normal The second method consists of terminating any course of corticosteroid therapy after very gradual dose reduction by giving ACTH gel every morning starting with 80 units and reducing by 20 units daily The first method is preferred.

During steroid therapy the recognized adjuvant methods should generally be used. These include

1 Salt restriction, the degree of which will vary with the cardiorenal status of the patient as well as with the steroids administered. With two of the newer steroids, methylprednisolone and triamcinolone, the need for salt restriction must be individually determined, as these agents do not produce salt retention in most patients receiving small dosages [60, 61] Salt retention may however be a problem when greater dosages are administered

2. An anti-ulcer regimen consisting minimally of antacids at frequent intervals between meals a bland diet, and frequent feedings of milk between meals. In addition anticholinergic agents may be utilized.

3. Supplemental potassium in the various forms available such as enteric coated tablets and 10 to 20 per cent syrups is also indicated in dosages averaging 5 to 10 gm per day in all patients receiving 10 mg of prednisone a day or more, or its equivalent.

4. Androgen-estrogen therapy to counteract the antianabolic effects of steroids.

It should be remembered that the newer steroids, while possessing less salt and water retaining effects, and less potassium excreting effect than older preparations, may in higher dosages possess these qualities to a clinically significant degree, and their use does not obviate the necessity of the use of appropriate adjuvant measures as noted above. This is particularly true when fluid retention is favored by preexisting cardiovascular renal disease.

Reifenstein [66] has recently recommended the combination of androgen with estrogen as the most practical anabolic preparation for the prevention or amelioration of osteoporosis resulting from the antianabolic effect of prolonged adrenocortical steroid therapy He has recommended the use of a combination of 90 mg of testosterone enanthate and 4 mg of estradiol valerate per ml of sesame oil given every 1 to 2 weeks [66] Also recommended in the management of osteoporosis in addition to androgen-estrogen therapy are adequate nutrition with generous amounts

of protein and calories, supplemental calcium, and as much activity as the patient can tolerate well [67 68]

Results

Merrell and Shulman have recently pointed out the many difficulties encountered in evaluating the prognosis in a chronic disease such as SLE, as well as the difficulty of assessing the influence of hormonal therapy on its course and prognosis. Conservative clinicians also agree that much additional experience will be needed before the final value of these steroids can be determined in so far as their effect on over-all prognosis is concerned [21] Although detailed statistical data are not available to substantiate the view at present, accumulated clinical experience indicates that the use of the adrenocorticosteroids does reduce morbidity and prolong life and may be lifesaving in the acute LE crisis [22, 23]

It is well recognized that SLE is a disease involving multiple systems. However involvement of a single organ or system may at times predominate the clinical picture. Therefore, from the standpoint of both treatment and prognosis it is of considerable important to the clinician to have an understanding of the potential influence of hormonal therapy not only on the over-all course of the disease but also on those signs and symptoms reflecting specific organ involvement. For this reason a brief review of pertinent experience regarding the value and influence of steroids with regard to specific organ involvement follows.

Skin. The cutaneous manifestations of SLE are generally improved within a period of 2 to 4 weeks of adequate steroid therapy [21] The toxic erythematous eruptions rapidly subside under such treatment, frequently leaving residual pigmentary changes, generally a mottled hyperpigmentation at the site of the previous eruption but occasionally depigmentation.

Joints [50, 51 53, 56, 63] The arthralgias and symptomatic nondeforming arthritides associated with SLE are among the earliest manifestations of the disease process to respond to adequate steroid therapy and usually subside within 2 to 4 days. More chronic changes disappear with amazing completeness

and within a few weeks muscle atrophy is much less evident. [50]

Lungs [70-72] The extraordinary frequency of pulmonary involvement has been stressed including the fact that pulmonary manifestations may be those which the patient initially presents [72] The most common pulmonary manifestation of SLE is pneumonia either lobar or patchy in distribution, presumably of bacterial cause, and in most cases responding to the usual antibiotic therapy The cause for the marked susceptibility to the development of pneumonitis in patients with SLE is not clear Cardasco et al. [71] have recently stressed the pulmonary manifestations of SLE and have pointed out that they can be the predominant clinical symptoms at any stage of the disease. The pulmonary findings may be of a bizarre nature and may simulate a variety of pulmonary lesions including pulmonary tuberculosis, and may provide a serious problem with regard to the decision as to whether or not to use steroids [63, 71] *Basically the treatment of the* pulmonic manifestations of SLE is that of steroids together with other appropriate measures including antibiotics. If the patient's clinical status permits, adequate steps should be taken to exclude definitely the presence of pulmonary tuberculosis before beginning steroid therapy Failure to demonstrate improvement of the pulmonary findings within several days of adequate steroid and antibiotic therapy demands reinvestigation from the standpoint not only of tuberculosis but of fungi and other causative agents.

A very common and annoying complaint is that of pain in the chest wall either to the right or left of the precordium. It is postulated that this pain is usually on the basis of a periostitis or a perichondritis, and has been found to respond better to salicylates and heat than to steroids [63]

Neurological Manifestations. Neurological manifestations of SLE are now known to be more common than was previously suspected, varying from acute toxic psychoses to so-called idiopathic epileptiform seizures, which may at times be the initial presenting symptom of SLE. Peripheral neuritis, blindness, hemiplegia, meningismus with pleocytosis, somnolence, neurogenic bladder dysfunction, and paraplegia are among the many other

nervous system manifestations which may appear in SLE [11 21 51, 53, 72] At times the clinician is confronted with the problem of differentiating neurological manifestations resulting from steroid therapy from those due to the underlying disease process. Seizures due to steroid therapy usually do not occur until well along in the course of the treatment and often not until a Cushing's state is reached. If activity of the disease is present as indicated by a recent exacerbation, or by the presence of fever and the patient is normotensive and has had no recent considerable weight gain, then the neurological symptoms are most likely to be due to the disease process and not to the steroid therapy and are indications for further steroid therapy [72] With the appearance of psychosis careful studies for the presence of hypopotassemia secondary to the steroid therapy should be made, and if definitely present or even strongly suspected, potassium therapy should be instituted. Precipitation of preexisting latent psychosis as a result of steroid therapy must also be considered.

Other causes of neurological manifestations include hepatic dysfunction, hypertension, and azotemia, intercurrent infections and meningitis due to *Cryptococcus neoformans*, tuberculosis, or other infectious agents. Untreated neurological manifestations of SLE pursue a variable course and once developed may be either transitory or permanent. Some do not respond to steroid therapy and when improvement does occur it is difficult to evaluate accurately the role of steroid therapy Some workers feel, however that there is no convincing evidence that steroids significantly alter the convulsive state due to active SLE [21]

Hematological Findings. A wide variety of hematological abnormalities may be observed in patients with SLE, some of which respond readily to adequate steroid therapy whereas in others the effect of therapy is variable.

ANEMIA. Anemia of varying severity may occur in patients with SLE. This anemia improves within a period of 1 to 4 weeks of adequate steroid therapy in most cases [21] However in those patients with concomitant renal disease, especially with azotemia, the anemia usually remains refractory to all treatment, and transfusions are often necessary [21 23]

The occurrence of acquired hemolytic anemia in association with SLE is well known as is the fact that it may be the initial manifestation of this disease [12, 21 73] The anemia in the majority of these patients responds well to adequate steroid therapy [12, 21, 53, 72] Splenectomy is of little or no value in treating this manifestation [21] and in some instances may be followed by development of overt manifestations of the disease [65] It has been postulated that the intact spleen may exert a controlling effect on the disease and splenectomy may lead to an exacerbation of the disease by removal of a possible controlling mechanism [73]

THROMBOCYTOPENIC PURPURA. Thrombocytopenic purpura has been observed in many cases of SLE and may be the presenting manifestation of the disease [13, 21 73–5] It may vary in severity from a moderate depression in platelets with associated purpuric skin lesions to a severe depression with widespread bleeding manifestations. The degree of severity of the thrombocytopenia determines to a considerable extent the measures to be employed in its management. If the platelets are not depressed to a level sufficient to cause clinical evidence of bleeding, a conservative approach to this facet of the disease may be taken, with periodic platelet counts and careful observation for bleeding being the main measures employed. However if the platelet depression is marked and the patient demonstrates clinical evidence of bleeding, despite adequate steroid therapy splenectomy must be seriously considered. Under such circumstances splenectomy has in general been successful in producing elevation of the platelet count and arrest of bleeding [13, 73–76] However it does not influence the other manifestations of SLE.

COAGULATION DEFECTS. Various coagulation defects have been observed often in association with hemorrhagic tendencies. These have included prolongation of clotting time, prolongation of prothrombin time and the presence of circulating anticoagulation factors. Such cases are unusual, and a large body of experience has not yet accumulated upon which to base a firm opinion as to the value of steroid therapy in the management of these problems. In the one patient we have observed, steroid therapy was of no

value. Harvey et al. [21] describe a single case in which steroid therapy was followed by a reduction in the titer but not a disappearance of the circulating anticoagulant factor. Swift et al. [77] describe two cases of SLE in which a circulating anticoagulant factor which acted to inhibit thromboplastin was found in the gamma globulin fraction of the patient's serum. In one case, in association with a steroid induced remission, this factor completely disappeared from the serum.

LUPUS ERYTHEMATOSUS (LE) CELL TEST. The LE cell test, which is still considered to be highly specific [78], cannot be used as an accurate guide of the effectiveness of therapy. It has been well documented [21, 22, 25, 31, 51, 56, 59] that steroid therapy sufficient to produce a clinical remission may leave the LE cell test unchanged, may diminish the number of LE cells present, or may cause complete disappearance of the phenomenon. In some instances this disappearance may be only temporary, and recurrence of a positive reaction to LE cell test may develop without evidence of clinical exacerbation of the disease. The concept that there is usually a direct correlation between the activity of the disease, especially fever, and the number of LE cells present has some support. Others [21, 25], however, feel that the number of LE cells present has no relation to the clinical status of the patient and that there is no correlation between the persistence of LE cells and the completeness of clinical remission.

BIOLOGICAL FALSE-POSITIVE REACTION TO SEROLOGICAL TEST FOR SYPHILIS. A biological false-positive reaction to the serological test for syphilis behaves similarly to the LE cell test in that it tends to be present more frequently in the more severe forms of the disease [6]. Its occurrence may wax and wane with the clinical course of the disease [7]. In other instances adequate steroid therapy appears to have little or no effect on the biological false-positive reaction [21].

ERYTHROCYTE SEDIMENTATION RATE. The response of the sedimentation rate to adequate steroid therapy is somewhat variable, but it usually decreases significantly in most patients [21, 23, 51, 58]. A return to normal of the sedimentation rate is usually associated with a complete clinical remission [21, 23, 58]. However, it

should be noted that the sedimentation rate may remain elevated despite an obvious clinical remission

SERUM PROTEIN ABNORMALITIES. Other serum protein abnormalities, including hypoalbuminemia, hyperglobulinemia, hypergammaglobulinemia, hyper alpha-2-globulinemia, elevated reaction to cephalin flocculation and thymol turbidity tests, revert toward normal in many instances on steroid therapy [21, 23] Reiner [79] found that the alpha-2-globulin tended to remain elevated despite reversal toward normal of other serum protein abnormalities with steroid therapy

Renal Manifestations. Involvement of the kidney in SLE has recently been reviewed in great detail by Muehrcke et al. [80] It is the opinion of this group of investigators that lupus nephritis is a progressive fatal, glomerulonephritis which at present is the main cause of death and the most serious problem in patients ill with SLE Its course may be fulminating, or it may develop slowly in a patient who has been ill for months or years. It may be the only overt manifestation of SLE. Clinical evidence of renal involvement is present in from two-thirds to three-quarters of patients with SLE, and pathological material shows an even higher incidence. In studying serial biopsies of 33 patients these investigators found no evidence of either regression or progression of structural damage as a result of steroid therapy and concluded that there is at present no way in which the development or progression of lupus nephritis can be prevented. They as well as others, however have observed clinical improvement of renal findings as a result of steroid therapy with a disappearance or decrease of abnormal findings in the urinary sediment, particularly in prolonged remissions [21 31, 51, 53, 58] On the other hand, some patients with severe lupus nephritis who have been given steroids have been observed to develop rapid elevation of blood pressure, together with rapid fluid accumulation to such a degree that discontinuance of hormonal therapy was necessary [21]

Cardiac Manifestations. It is of interest to note that in those patients with coexisting renal disease pericarditis and myocarditis due to lupus tend to follow the same course as the renal disease.

However in those patients in whom renal disease is absent, the pericarditis, myocarditis, and pericardial effusions tend to respond to adequate steroid therapy within 1 to 3 weeks [21, 51]

OTHER TYPES OF THERAPY

Nitrogen Mustard

Nitrogen mustard has been used by several investigators [21, 31, 55, 81] in the treatment of SLE since the original publication of its success in the treatment of glomerulonephritis in 1949 by Chasis Goldring, and Baldwin [82, 83] Its use was based on its possible influence on hypersensitivity states, in view of its known ability to inhibit antibody production [21] Dubois [55, 81] has obtained good results with its use particularly in the SLE patient with the nephrotic type of nephropathy with diuresis, decreased proteinuria, return of serum proteins toward normal, and decrease in nonprotein nitrogen following its use. He achieved no improvement in nonedematous hypertensive patients with or without nephropathy or in patients with active SLE and normal renal function, and suggests that the time to administer nitrogen mustard is after 2 months of steroid or other therapy which adequately controls other manifestations but leaves a nephrotic picture with edema and with or without nitrogen retention. He utilizes a single intravenous dose of 20 mg and has had no serious toxic reactions. Haserick [31] described a dramatic response to combined nitrogen mustard and steroid therapy in a single case with reversal of the LE cell test phenomenon, resulting in a remission which had continued for 6 years at the time of publication. After this initial experience he treated another 35 patients, one of whom succumbed to agranulocytosis. The dosage was reduced in the remaining cases, all of which demonstrated neither severe side reactions nor dramatic improvement. Harvey [21] relates a case in which a patient received two courses of nitrogen mustard because of an erroneous initial diagnosis of lymphoma. She showed no immediate improvement but did experience two subsequent periods of symptomatic relief. However over a 2-year period the SLE progressed to involve the joints and kidneys. He

concludes that the use of nitrogen mustard in SLE does not appear to be therapeutically promising and is potentially hazardous [21]

Para-aminobenzoic Acid

Light sensitization is known to occur at times both in patients with SLE and in individuals receiving a sulfonamide drug, and because para aminobenzoic acid is a metabolic antagonist to sulfonamides it has been employed by a few investigators in the treatment of SLE. Zarafonetis [84, 85] treated six patients with acute SLE with para-aminobenzoic acid and observed a good response in only one case. He further noted that the reactions to para aminobenzoic acid were more frequent in lupus patients than in other patients with other diseases treated with the same drug Johnson and Meyer [86] noted both objective and subjective improvement in four of five patients treated with para-aminobenzoic acid, but this was not sustained in each instance Each patient later received cortisone, and the authors concluded that the response to cortisone therapy was more rapid than with para-aminobenzoic acid therapy Harvey [21] noted a severe exacerbation of renal manifestations coincident with para-aminobenzoic acid administration. Para-aminobenzoic acid is rarely used today either singly or adjunctively in the treatment of SLE.

Hemotherapy

Kurnick [8] has proposed the use of small fresh whole blood or leukocyte transfusions in the therapy of SLE as a source of needed deoxyribonuclease inhibitor He postulates the development of an abnormal factor in the gamma globulin fraction of serum, which increases the permeability of mesenchymal cells to serum proteolytic enzymes, which then enter the cell and destroy deoxyribonuclease inhibitor with the subsequent depolymerization of the nuclear deoxyribonucleic acid, and cell death and associated inflammatory reaction follow He states that the deoxyribonuclease inhibitor supplied by the intramuscular injection of small amounts of fresh whole blood or leukocytes prevents this

sequence of events. He summarizes his results from the treatment of eleven patients as "good" in seven cases, "doubtful" in two cases, and "poor" in two cases. Improvement is evidenced by disappearance of LE cells, fever, arthralgias, pruritus, pericarditis, myalgias, and improvement in urinary function within a period of 3 to 6 weeks, and he states that "... continuous therapy has maintained patients in remission for a number of months ... and may permit marked reduction or complete withdrawal of steroids. He feels that "... the procedure is quite safe ..." and should be given additional trial.

Although this theory of the pathogenesis of SLE is an intriguing one, the exact value of this mode of therapy is still to be determined.

Recent studies utilizing fluorescent antibody techniques lend some support to this concept by suggesting that the LE serum factor has an affinity for nuclear nucleoprotein and that deoxyribonucleic acid is involved in the bond. The authors raise the question as to whether the LE serum factor which migrates with gammaglobulin could be an autoantibody to nucleoprotein or DNA [88]

Perhaps the most useful drug other than hormones in the management of SLE is acetyl salicylic acid. [21] Salicylates in patients with SLE produce rapid defervescence in more than one-half of the cases [23] However in many patients no response occurs even with high doses. In some individuals joint pains will remit as the fever decreases on salicylate therapy However in others arthralgias may persist despite disappearance of fever while in still others arthralgias remit with no change in fever [21] It has been recommended that in those patients with SLE presenting a mild rheumatoid arthritic or rheumatic feverlike picture bed rest and salicylates to the point of salicylism should be given an initial therapeutic trial before employing more vigorous methods [55] In addition to being the major drug to be employed in selected cases in which steroid therapy is contraindicated (e.g., profound psychosis on steroid therapy) salicylates are useful in relieving myalgias, arthralgias, and the diffuse aches and pains present in many patients [22]

Antimalarials

In 1940 Prokoptchouk [89] introduced the use of quinacrine (mepacrine, Atabrine) in the treatment of discoid lupus erythematosus stimulating further study in this country and abroad. Page in 1951 reported on the use of quinacrine in 18 patients, 17 with chronic discoid lupus erythematosus and 1 with SLE, and noted beneficial results in all patients [90] Since then the anti malarial drugs including quinacrine (Atabrine, mepacrine) chloroquine (Aralen) hydroxychloroquine (Plaquenil) and amodiaquin (Camoquin) have become recognized agents of choice in the treatment of chronic discoid lupus erythematosus and have been given clinical trial in the treatment of SLE by many workers [22, 31 55, 56, 90–93] Because their effect is too slow in onset, they are not suitable as the sole agents for the treatment of acute episodes of SLE, although they may be used adjunctively with the steroids in this situation [31] Reports of their value in SLE are somewhat variable, but in general they appear to be more effective and to produce more improvement in the less active low grade systemic cases, and are less effective in the more active virulent forms of the disease [31, 56, 91] Their use is recommended primarily in the milder cases of SLE, especially in those cases with a definite cutaneous component [31 55] Most authors agree that the antimalarials are of value in selected cases as adjuncts to steroid therapy permitting greater decrements in needed maintenance dosages [22, 56, 91–93] Dubois [91] emphasizes the value of antimalarials in maintaining remission on lower steroid doses, or without steroids, for periods sufficient to allow some reversal of the osteoporosis, peptic ulceration, negati e nitrogen balance, and other changes resulting from long-term adrenal steroid therapy

Side effects of this group of drugs include severe nausea and vomiting, diarrhea, personality changes, psychosis, convulsive seizures, myasthenia, lichenoid, exfoliative, and other dermatitides, pruritus, yellow staining of the skin (Atabrine) anemia, thrombocytopenia, leukopenia, headache, cycloplegia, graying of the hair and lassitude [31, 55, 56, 90–95] Severe side effects

necessitate reduction or complete withdrawal of the drug, and milder side effects demand close observation and reduction of dosage to forestall more serious side effects. Inasmuch as these drugs are cumulative in effect, toxic side effects may persist for some time following withdrawal of the drug. Caution must be exercised in using the antimalarials as emphasized by several reports of fatal aplastic anemias resulting from the use of Atabrine [23]

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John A. Hosmer **2**

DISCOID (CUTANEOUS) LUPUS ERYTHEMATOSUS

DISCOID LUPUS ERYTHEMATOSUS is a chronic progressive, cutaneous disease occurring in a localized and widespread, sometimes termed the chronic disseminated, form. In the former lesions appear on the scalp, ears, face, and lips, while in the latter type, in addition to these areas, there is involvement of the sides and \ of the neck, the thorax, the arms, the hands, and, occasionally other areas. The early lesions may be single or multiple and are erythematous macules or edematous plaques, with more or less adherent scales. The lesions increase in size gradually and may in the course of months develop into ovoid plaques, 1 cm or more in diameter These plaques usually show central atrophic scarring, prominence and plugging of the follicles, telangiectasia, pigmentary changes, and, on the scalp alopecia. There may be coalescence of plaques to involve extensive areas.

GENERAL STUDY OF PATIENT

In discoid lupus erythematosus the general health is usually good, and the laboratory examinations are normal or nearly normal. The only complaint is, as a rule the visual presence of

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seborrheic dermatitis, rosacea, and, sometimes psoriasis, sarcoidosis, lupus vulgaris, superficial epitheliomatosis, and others. Diagnosis may present no problem but at times may confound the expert.

EVALUATION OF THERAPY

Statistical evaluation of any form of therapy is difficult because of the unpredictable course of the disease, remissions and relapses occurring with greater or less frequency Unfortunately there have been available no data of consequence on the natural history of lupus erythematosus. Recently studies have appeared which are being carefully documented but from which at present only inferences can be drawn [6–8] Spontaneous involution occurs perhaps more commonly than we know occasionally leaving few residuals but more frequently terminating in the characteristic atrophic scars and alopecia. The type of lesion has no prognostic value, but the behavior of the lesion has [2] As a rule, the presence of a small number of lesions which progress slowly and become atrophic early indicates that the patient has the power to control the disease, whereas continued appearance of small lesions, particularly if they appear on areas other than the face, indicates poor resistance The duration, severity and extent of the disease usually condition the therapeutic results This is not invariably so since a single lesion can be more resistant to treatment than numerous small lesions [2] In general, those with widespread, chronic, thickly scaling lesions present a great problem, since they often do not respond to any therapeutic measure. Patients who have only the residual inactive scars of discoid lupus erythematosus require no treatment, since these cannot be altered by available systemic therapy In all instances treatment must be individualized and must not be worse than the disease

Treatment is preferably instituted early in the attempt to heal the lesions as quickly as possible, thus preventing their extension and minimizing scarring. The treatment of discoid lupus erythematosus is either systemic, topical or a combination of both. All remain on a purely empiric basis, and none is capable of clearing or curing all cases. None of the effective systemic methods is

unquestionably safe, a fact which requires the exercise of constant clinical and laboratory wariness.

ANTIMALARIALS

The synthetic antimalarials have been the object of interest and investigation as therapeutic agents in the treatment of discoid lupus erythematosus for the past half dozen years. The stimulus was a report by Page in 1951 concerning the usefulness of quinacrine hydrochloride (Atabrine) [9]. His investigation was made independently and without awareness of the fact that Prokoptchouk, a Russian, had made the same observation in 1940 [10]. The application of antimalarials to forms of lupus erythematosus was not new. In 1894 quinine was first suggested for conditions, including lupus erythematosus, which are characterized by vascular congestion, and in 1928 there was reported a beneficial effect in 22 of 28 cases of discoid and subacute lupus erythematosus treated with the synthetic antimalarial pamaquine (Plasmoquin) [cited by 27]. Experience with this latter drug during World War II indicated that it is not as safe as quinacrine [34] and it is not now recommended in lupus erythematosus.

Quinacrine. The efficacy of quinacrine was soon further confirmed by numerous observers both here and abroad [11–25]. The dose customarily has been 0.1 gm daily after a significant degree of improvement has been noted. As a rule, lessening of the erythema, edema, and thickening of the affected areas has been observed within the first 4 weeks, if the eruption is at all amenable to the drug. Treatment is continued for at least 4 weeks after the last traces of activity have disappeared. As an over-all average, it is felt that about 40 per cent obtain excellent results, 35 per cent moderate improvement, while 25 per cent do not obtain any benefit or become worse. It soon became apparent that in many instances the beneficial effects are temporary, 80 per cent having relapsed at the end of 1 year [23]. Almost all the relapses again improved on a repeated course of the same medication.

The administration of quinacrine is accompanied by side effects, some of which are mild and some potentially hazardous. Therapeutic doses of the drug over the necessary period of treat

ment frequently produce a characteristic unpleasant yellowish discoloration of the skin. Originally this was thought essential to a salutary result, it being later observed that benefit frequently precedes this occurrence and, consequently is probably unrelated. Side effects involving the gastrointestinal tract, the liver the central nervous system, the hematopoietic system, and the skin have been reported. Nausea, vomiting, diarrhea, dizziness, headache, and mental depression have at times been severe enough to require discontinuance of the medication. Serious complications consisting of toxic psychosis, aplastic anemia, agranulocytosis, and dermatitis of the lichenoid, eczematoid, or exfoliative type are less common. Some are of the opinion that patients suffering from lupus erythematosus are unusually liable to develop skin complications from any treatment. To corroborate this impression they cite the fact that Page observed a 10 per cent incidence of dermatitis in 62 quinacrine-treated lupus erythematosus patients. However this is about the same rate of occurrence as observed in the Southwest Pacific in troops on long-term Atabrine antimalarial prophylaxis [35] Certainly the possibility of producing a dermatitis potentially more prolonged and disabling than the original discoid lupus erythematosus exists with quinacrine.

In the effort to find drugs more efficient and less toxic than quinacrine, other antimalarials were investigated. Chloroquine diphosphate (Aralen) amodiaquin hydrochloride (Camoquin) *pyrimethamine* (*Daraprim*) *chloroguanide acetate* (*Paludrine*) and hydroxychloroquine (Plaquenil) have been tried. Chloroquine, amodiaquin, and Plaquenil are effective. Paludrine and Daraprim, which latter incidentally is hazardous [36] do not have any therapeutic efficacy in lupus erythematosus [28, 37] This points to the fact that the effectiveness of certain antimalarials is related to some quality independent of antiplasmodial activity

Chloroquine. Chloroquine was found to be at least as effective as, productive of fewer side reactions than, and less toxic than quinacrine. It is now the generally preferred drug [24–33] The average dose is 250 mg twice daily for 1 to 2 weeks, followed by

250 mg daily An improvement is generally discernible within 2 weeks, and it is doubtful if any effect will be noted if it has not appeared after a month's treatment. If at the end of a month's time, the signs of the disease in the skin are involuting markedly and steadily it may be possible to reduce the dose to 250 mg given every other day or every third day for some weeks. When signs of the disease have disappeared completely or if the residual lesions seem quite quiescent, treatment is stopped. It is well to remember that when the lesions of chronic discoid lupus erythematosus become quiescent, they may remain so for many months or even years. On the average, the results have been excellent in about 33 per cent, very good in 25 per cent, good in 25 per cent, with failure in the remainder In many it will be found that the reduction of the dose below an individual maintenance level will be followed in 2 to 8 weeks by a recurrence of discoid lesions. In these cases a maintenance dose, which may be as little as two tablets weekly in some, must be individually determined and may have to be continued indefinitely

The side effects from chloroquine are sometimes significant. Those reported have included pruritus, nausea, anorexia, diarrhea, headache difficulty in visual accommodation, weight loss, bleaching of the hair hair loss, lichenoid dermatitis, urticaria, morbilliform eruptions and methemoglobinemia. Two instances of porphyria [38, 39] have been observed concomitant to the administration of chloroquine, one of which was felt to represent a curious coincidence of a patient having both porphyria and chronic discoid lupus erythematosus [40]

Amodiaquin. Amodiaquin hydrochloride is a derivative of chloroquine It has been used in some patients who were intolerant to or failed to respond to, other methods of treatment, being administered in doses of 200 to 400 mg daily [26, 41 42] The drug is less promising generally than chloroquine but may be tried where chloroquine has been ineffective. The symptoms of intolerance have been those of a mild gastrointestinal nature however recently Parkinsonian like tremor associated with anxiety and tension and convulsive episodes have also been reported. Neurological complications certainly might be expected

from the antimalarials and have been reported ranging from mild to major proportions [42]

A significant number of patients receiving quinacrine and chloroquine derive little or no benefit from them, either because of side effects of sufficient severity to compel discontinuance of medication, or simply because of lack of therapeutic effect. For this reason Plaquenil, another derivative of chloroquine, was investigated [43–46] It is about one-fifth as toxic as chloroquine it is absorbed more rapidly and gives blood levels several times higher than chloroquine. The usual dosage range is from 200 to 800 mg daily with a treatment duration of from 3 to 6 weeks. The drug, as is also true of chloroquine and amodiaquin does not produce staining of the skin. It occasionally produces gastrointestinal symptoms, sometimes requiring temporary discontinuance. Nervousness, hoarseness, morbilliform eruptions, pigment loss and blonding of the hair have been reported. Plaquenil's principal usefulness appears to be that it can sometimes produce further improvement often substantial, after the effects of sister antimalarial drugs have come to a standstill. It is sometimes tolerated by patients who have been previously intolerant to other antimalarial medication.

As has been indicated, some patients are treatment-fast to one antimalarial and may be benefited by another Others initially improved may come to a standstill and substitution of another drug may result in further improvement. This has lead to the exchange sometimes in the same patient of quinacrine, chloroquine, Plaquenil, occasionally amodiaquin, and sometimes combinations of the drugs have been used. Recently a preparation, APA 5533, which contains in each tablet one-fourth of the usual therapeutic dose of quinacrine (25 mg) Plaquenil (50 mg) and chloroquine (65 mg) was reported [47] This combination was used because no drug is effective for all patients, and it was hoped that there might be an increase in therapeutic efficacy and a decrease in untoward reaction if smaller amounts of all three antimalarials were combined. It also was thought possible that such a combination might induce a synergistic therapeutic effect. The study embraced 10 patients with discoid lupus erythematosus

to whom doses ranging from eight to twelve tablets daily were administered. Seven had an excellent result with complete subsidence of all clinical activity. There was no response to a daily dose of eight tablets in the remaining three patients, but an excellent improvement in each was noted when dose was increased to twelve tablets daily. At the end of the first week the dose was reduced to eight tablets and the following week to a maintenance dose of four tablets daily. Two remained completely clear after several weeks of this maintenance dose, while the third patient developed a recurrence on this decreased dosage. Only three patients had intolerable side effects, two of whom had severe diarrhea, dizziness, and muscle pain on a dosage schedule of eight tablets, the third developing a severe diarrhea when on twelve tablets a day. The remaining patients are said to have had no complaint or only a minimum discomfort with mild diarrhea, diplopia, nausea, and vertigo and in these instances it was not necessary to discontinue therapy. Some of these patients had had marked side effects from previous antimalarials in the usual dosages. The feeling of these investigators was that the combined tablet produced better results and was better tolerated than any of the three medications taken individually. It will be noted that the doses are large, the total intake of antimalarials ranging from about 1,200 to about 1,700 mg per day. Further experience is necessary to evaluate such combinations.

Mechanism of Action. The mechanism of action of the antimalarials is not known. The original feeling that it might be based in part, at least, on a light screening effect due to deposition of these drugs in the horny layer or in the epidermis is now believed to be erroneous. It has been shown that chloroquine modifies certain abnormal but not the normal responses of skin to ultraviolet light in the sunburn spectrum [48]. Antimalarials have an antiinflammatory effect in subjects with lupus erythematosus, as well as other diseases such as rosacea, and in rheumatoid arthritis. Whatever the mechanism, all have seen lesions disappear, even hypertrophic plaques may melt down and atrophic plaques grow some hair. Specimens for biopsy taken from a successfully treated case present a microscopic picture that

frequently does not resemble lupus erythematosus at all [49]

The oral administration of the antimalarials is clearly only *palliative* [5] *in discoid lupus erythematosus. Granting even that* the majority of patients initially respond favorably the length of time remissions will endure is unpredictable and is unrelated to the amount of treatment which precedes them [20] Most relapses occur in the first few months, although some are delayed, the disease having recurred in the majority of patients within 2 years. This indicates that the permanent cure obtained in a few cases is due to a supportive effect on reparative processes already taking place [26] It is increasingly apparent that a maintenance dose, adjusted to the individual patient's requirement will have to be used for months, perhaps years. Recent observations suggest that maintenance doses less than used under therapy do not seem to suppress relapse to any great extent [32]

HEAVY METALS

Heavy metals have been used in the treatment of discoid lupus erythematosus for many years. Arsenic in the form of Mapharsen is probably now used little, if at all. Gold and bismuth retain a place in the management of the discoid disease, although there is sharp division of opinion regarding the hazards and effectiveness [2, 20, 27 51] of their use. Bismuth is less toxic than gold, produces fewer untoward reactions, and is administered with greater ease than gold but its action is slower and less certain. The more common form of administration is intramuscularly in the form of bismuth subsalicylate in oil in doses of 0.2 gm weekly Tablets of Bistrimate (bismuth sodium triglycollamate, each tablet representing 75 mg of metallic bismuth) may be given in doses of three to six tablets daily in divided doses after meals. There is argument regarding the relative efficiency of the two routes [52] the intramuscular being generally preferred. In all forms of bismuth therapy a bismuth line may develop, which may be obviated by careful oral hygiene, and toxic symptoms of stomatitis diarrhea, and depression of the white blood cells may occur Serious difficulty can be avoided by careful attention to the patient and periodic blood examinations. Some [53] believe that bismuth is

still surprisingly effective in both discoid and relatively mild subacute systemic cases. In large degree, bismuth has been displaced by the antimalarials. However in an occasional case, only slowly responsive bismuth seems sometimes to be definitely adjuvant when given concomitantly

Gold. The disparity of opinion with regard to gold is even more vehement. Some dermatologists have entirely abandoned gold in the treatment of discoid lupus erythematosus in the belief that it is too toxic and/or that it is not particularly effective [2, 27] Others [51] believe that treatment with gold in the form of gold sodium thiosulfate produces longer-lasting remissions than with any of the antimalarials alone that improvement is hastened materially when gold is added after the first erythematous phase has subsided, perhaps following the use of antimalarials and that there are numerous cases otherwise treatment fast which respond to the use of gold. The antimalarials have markedly reduced the indications for gold therapy by reason of their superior rapidity of action, in those cases where they are effective, and their relative freedom from toxicity Treatment with gold should be considered only in selected patients resistant to adequate trial of more conservative forms of therapy Systemic lupus erythematosus, tuberculosis, liver and renal disease are absolute contra indications.

Gold may be injected intramuscularly as gold sodium thiomalate (Myochrysine) or aurothioglucose (Solganal) but is more commonly used as gold sodium thiosulfate administered intravenously The initial dose is 2 to 5 mg which is increased weekly by 5 mg until a response is obtained, or until a weekly dose of 50 mg is reached. In general, improvement should be clearly apparent by the end of the fourth or fifth injection. If there is only slight or indefinite benefit at the end of eight or ten injections in the dosage recommended, it is probably profitless to continue. Careful check of the leukocyte count and of the urine should be made frequently One should always keep in mind the fact that gold therapy constitutes a certain risk and should be terminated at the first sign of an undesirable reaction. Pruritus and leukopenia are the initial signs of intolerance and careful attention to

these, particularly to the symptom of itching, will minimize any potential difficulty [54] Toxic reactions caused by gold therapy are of the type caused by other heavy metals and consist of urticaria, exfoliative dermatitis, leukopenia, agranulocytosis, nephritis, and hepatitis [55] It is the general consensus that those who have used much gold in the past in treatment of chronic discoid lupus erythematosus are likely to have encountered far more serious side effects from gold than they are now experiencing with the antimalarials [56] Toxic effects usually follow the administration of a considerable amount of gold, although it may appear very early [55] Adverse effects in as many as 22 per cent have been reported. Others of wide experience have yet to see any toxic effects, dermatological or otherwise, from the use of intravenous gold sodium thiosulfate in doses of 50 mg or less per week [51] The effectiveness of gold as reported in discoid lupus erythematosus varies, in general being said to produce the same relative number of remissions as the antimalarials [56]

OTHER AGENTS

Many other systemic agents have in the past had their advocates Among these have been some of the antibiotics [57 58] isonicotinic acid hydrazide (INH) [64, 65] calcium pantothenate [59] Panthenol [59, 60] the tocopherols [59, 61] derivatives of para aminobenzoic acid [62] vitamin B $_{12}$ [63] and crude liver extract. Most of these have had doubtful efficacy were prolonged and expensive, or were productive of unpleasant and sometimes toxic effects. The intramuscular injection of crude liver extract or vitamin B seems occasionally to be useful in conjunction with other treatment, although the benefit is difficult to assess. PABA in doses of 3 gm daily considerably less than formerly recommended, has been reported beneficial in combination with the antimalarials [66]

The steroids and adrenocorticotropic hormone (ACTH) have been used in discoid lupus erythematosus with suppression of the inflammatory portion of the process. Relapse promptly follows their cessation. These materials have no place as a prophylaxis, and it is generally agreed that they should not be used in discoid

lupus erythematosus, even though extensive and associated with mild systemic symptoms.

TOPICAL THERAPY

Topical treatment of discoid lupus erythematosus is of relatively minor importance. It is usual to prescribe one of the sun-protective preparations, to which may be added 1 or 2 per cent bentonite or Neutracolor to provide a masking effect. A proprietary preparation satisfying these requirements is A Fil cream and Sun Stick. The subcutaneous injection of hydrocortisone acetate solution is said to be occasionally useful. Obliteration of the local lesion has been attempted by a variety of topically applied agents, including solid carbon dioxide, liquid oxygen, liquid nitrogen, and 90 per cent phenol none of which has been entirely satisfactory Perhaps the best is freezing the lesion with solid carbon dioxide to produce a reaction just short of blistering, an effect requiring practice to achieve. Such local treatment does not prevent scarring, which is a usual result of the disease, and often may accentuate it. Early lesions of the erythematous or edematous type often heal spontaneously and external application in these should be bland [2] Ultraviolet irradiation is to be avoided for obvious reasons. X-ray and radium are not used, since they are without beneficial effect.

The general health of patients with discoid lupus erythematosus should be supervised. Their other illnesses, including the trivial, assume a somewhat different proportion than is true of the general population Caution with regard to the use of drugs, antibiotics, and biologicals is indicated. It is generally advised that accessible foci of infection, such as those about the teeth, be eradicated at some quiescent stage. These patients should avoid excessive exposure to sunlight, but almost all do not and need not curtail outdoor activity if they observe reasonable precautions. It is apparent that light is only one of a number of trigger factors in discoid lupus erythematosus the season, and emotional, immunological and other biological agencies may exert an influence, although many patients undergo these and other traumatic episodes without untoward reactions [2]

SUMMARY

There is no specific or entirely successful treatment for discoid lupus erythematosus. The antimalarials as used at the present time are only suppressive; they are the least toxic of the effective measures, and, generally they are more effective than older methods. Chloroquine is the drug of choice. Plaquenil, amodiaquin, and quinacrine are occasionally useful, and antimalarial combinations may have some value. Bismuth and gold retain some, but limited, value in selected patients.

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William N Piper

3

GENERALIZED SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

In this presentation it is not our purpose either to review the literature or to discuss the etiology but rather to discuss the known features of this not uncommon but bizarre disease. However because of the many outstanding contributions, a brief review of the history of scleroderma is considered essential.

CLINICAL FEATURES

The earliest descriptions of the disease are credited to Diemerbroeck in 1660 and to Lusitanus in 1634. Beerman [1] stressed the protean nature of the disease in an excellent review of the literature Becker and Obermayer [2] defined the disease as follows

> Generalized scleroderma is not strictly a dermatosis, but rather a disease of the connective tissue of various organs and systems, the skin, subcutaneous tissue, muscles, bones and joints, tendons and fascias, serous surfaces, internal organs, endocrine glands and nervous system. The patient first notes the surface alterations, consequently the dermatologist is usually first consulted.

Goetz [3] has suggested the term *progressive systemic sclerosis* to describe the clinical picture until a cause has been established. He has ably described the disease as follows

> Progressive systemic sclerosis may be defined as an induration and sclerosis which may occur in any organ, including the skin muscles and blood vessels. Pigmentation, loss of weight, asthenia, arthritis and other symptoms occur depending on the degree and extent of the sclerosis. Everywhere the same changes occur viz., edema, followed by proliferation of connective tissue and sclerosis of collagenous bundles, resulting in many cases in atrophy of the organ concerned This may occur in the connective tissue of the skin, in the interstitial tissue between the alveoli of the lungs, in the acini of the liver in the kidney in the muscle fibers of the heart, within the pulp of the spleen and in the endocrine glands.

O'Leary and Waisman [4] confirmed the previous work of Hutchinson and Sellei [5–13] to establish the clinical syndrome of acrosclerosis and further stressed the visceral manifestations existing in this entity

Leinwand and associates [14] from a clinical study of over 150 cases, concluded that scleroderma is a disease of the mesenchyme of unknown etiology and that the symptoms and findings vary according to the location of the tissue involved.

The clinical features of a fully developed case of generalized scleroderma are easily recognized, however the early diagnosis may be difficult.

In that early diagnosis and subsequent early and adequate treatment offer these unfortunate patients the most favorable prognosis, a brief review of the course and protean nature of this disease is indicated.

Four clinical variations of scleroderma are usually described morphea, circumscribed linear (coup de sabre) and generalized scleroderma. In this presentation, only the latter will be considered.

Clinically cutaneous alterations may be present for months before medical aid is sought. The progressive involvement of the skin is characterized by three clinical stages In the first there is edema in which the skin usually has an ivory yellow white appearance with flattening of the normal folds of the skin. In the

second stage the edema is replaced by fibrosis. In the third stage, atrophy and contractures exist. These may affect both the mucous membranes and the glabrous skin.

PATHOLOGY

Pathologically the basic feature in scleroderma appears to be fibrinoid degeneration of the collagen fibers. These changes, consistent with scleroderma, have been reported in almost every



Fig 3-1 Typical Raynaud' phenomenon in scleroderma, with dystrophic changes of the fingers (Courtesy of *Armed Forces Institute of Pathology.*)

organ or system. Early involvement of small veins and arteries has been described. A decrease in the ganglion cells of the myenteric plexus of the gastrointestinal tract has also been described. Virtually all the endocrine glands, especially the parathyroid, have been involved.

Systemic scleroderma is not a rare disease. It is usually seen in the fourth and fifth decades of life, although several incidents

in children have been reported. It is more frequent in females. The age of onset was found usually to be earlier in females than in males, and the duration from onset to death is shorter for females than for males. The duration of the disease is longer in the presence of Raynaud's phenomenon (Fig. 3-1) In general, no conclusive hereditary factor or consistent associated disease or diseases have been determined to be associated with this entity

Clinically the skin of the face, hands, and forearms especially and less frequently that of the feet and ankles, is usually involved. This may progress to involve almost the entire body

MECHANISM OF DEATH

In a recent review of 31 necropsies [15] the primary cause of death in all patients was difficult to determine, as in many of the patients death could be attributed to more than one factor The mechanism of death was associated with the following

Cardiac conditions	9
Renal failure	5
Cachexia	5
Terminal complications	4
Pulmonary insufficiency	6
Hypertension	–
Duodenal ulcer with hemorrhage	1
Esophageal-pleural fistula	1
Sarcoma with metastases	1

In this series the incidence of systemic involvement as confirmed by pathological examination was

Tissue	*Per Cent*
Skin	100
G.I tract	64
Heart	90
Kidney	74
Lungs	90

SYMPTOMS AND SIGNS

It was of interest to find that the initial sign or symptom in eight, or approximately 25 per cent, of the patients, later confirmed by pathological examination, was attributed to involvement of systems other than the joints or skin. The lungs were so involved in five patients, the kidneys in two, and the heart in one.

Conversely two patients with cardiac and two with pulmonary involvement had neither diagnostic signs nor symptoms referable to these systems reported. Pathology consistent with scleroderma was found in these tissues at necropsies



Fig. 3-2. Both the small and large joints are involved early in the course of scleroderma. (Courtesy of Armed Forces Institute of Pathology.)

In this series (Fig. 3-2) the onset was characterized by joint symptoms which occurred either concomitant with or during a period extending up to 1 year prior to the recognition of other signs or symptoms, both the large and small joints were affected at the same time.

The second most frequent initial symptom was involvement of the skin. Terminally the entire body was involved in 52 per cent of the patients It is of interest that none of the patients had skin lesions initially described or diagnosed as circumscribed

scleroderma which subsequently progressed to that which is characteristic of generalized scleroderma. Necropsies of an additional 17 patients with lesions of circumscribed scleroderma whose primary cause of death was attributed to causes other than that



Fig. 3-3. Progression of scleroderma. The upper third of the esophagus is dilated with barium remaining on the walls. Its distal third is characteristically constricted. Shortening of the esophagus has produced hiatus hernia. Annular narrowing of the pars media of the stomach was present in all films. (Courtesy of *Armed Forces Institute of Pathology.*)

of generalized scleroderma were reviewed in no instance was either clinical or pathological evidence of visceral involvement reported or observed. Leinwand, however has reported one patient with circumscribed scleroderma which subsequently progressed to generalized scleroderma.

With progression of the disease (Table 3 1) the gastrointestinal tract (Figs. 3-3, 3-4) and heart, the kidneys, and the lungs (Fig. 3-5) in that order of frequency were further involved. The lungs were *rather consistently involved throughout* the entire course.

Seventeen of the patients had associated Raynaud's phenomenon. In these patients, joint symptoms and skin lesions in general occurred earlier were more extensive, and were followed by early concomitant involvement of the gastrointestinal tract, heart, kidneys, and lungs. As the disease progressed, the heart, kidneys, and lungs, in that order were further involved.

In those patients with Raynaud's phenomenon, involvement of the individual viscera was more slowly progressive. Initially the predominant visceral lesions were of the gastrointestinal tract and heart. As the disease progressed, the kidneys and lungs in that



Fig. 3-4. Progression of scleroderma. Alternating dilatations and constrictions of the small bowel are characteristic, with the walls serrated indicating possible mucosal ulceration. (Courtesy of Armed Forces Institute of Pathology.)

order of frequency were further involved. The percentage of specific visceral systems involved with scleroderma at necropsy in patients without Raynaud's phenomenon was higher than in those with Raynaud's phenomenon.

The symptoms of joint involvement are not in general diagnostic but include stiffness, restriction of movement, pain and swelling, redness with heat, characterized by exacerbations and remissions. Both the large and small joints are usually involved.

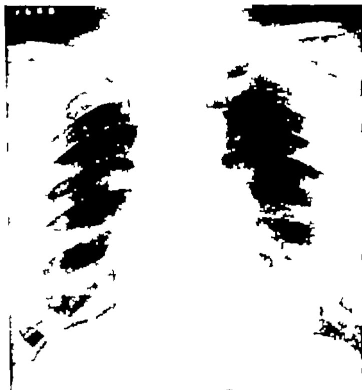


Fig. 3.5 Progression of scleroderma. Generalized pulmonary fibrosis. (Courtesy of Armed Forces Institute of Pathology.)

Early skin involvement is characterized by swelling, tightness, thickening, tenderness, and redness, in addition to the usual ivory white shiny appearance of the skin and distribution which is seen later

In most instances, it is difficult to differentiate between the

Table 3-1 PATHOLOGICAL AND CLINICAL INCIDENCE AND SEQUENCE OF SYMPTOMS IN GENERALIZED SCLERODERMA (31 PATIENTS)

	Pathological incidence		Clinical incidence		Sequence of reported symptoms					
Site	Total	%	Total	%	1st	2d	3d	4th	5th	6th
Joints			80	97	(19)	9	2			
Skin	81	100	31	100	11	(16)	2	2		
GI tract	20	64	30	97	1	4	(13)	(7)	2	3
Heart	28	90	30	97	2	6	(10)	(9)	2	1
Kidneys	23	74	30	97	2	1	7	(7)	(8)	(4)
Lungs	28	90	29	93	4	5	5	5	(7)	(3)

NOTE Numbers in parentheses highlight the relative frequency of occurrence of the sites of involvement.
SOURCE W N Piper and E B Helwig [5].

complaints referable to the heart and to the lung. The symptoms most frequently associated with the heart were dyspnea, ankle edema, cyanosis, cardial enlargement, distended neck veins, signs of pericardial fluid, and friction rubs and precordial pain. Cardiac murmurs reveal, usually no consistent location. In general, cardiac diseases usually fell into three general types cor pulmonale with prior pulmonary involvement, cardiac degeneration, and various arrhythmias. At least two patients have been reported with complete heart blocks.

The electrocardiogram is neither consistent nor diagnostic of scleroderma heart disease. However serial electrocardiograms are helpful in detecting cardiac changes. Sinus tachycardia, *arrhythmias, disturbance of conduction, and decrease in voltage* constitute the commonest findings.

Complaints usually associated with gastrointestinal tract involvement are anorexia, nausea and vomiting, abdominal pain, constipation, fullness or distention, and dysphagia.

Renal signs and symptoms are rather vague and nonspecific. Abnormal urinalysis with albuminuria and mild to moderate oliguria are usually the first findings. Later azotemia and death occur

An increase in temperature is usually present at one time or another and is usually an intermittent and low grade type except when other complications are present.

The entire course of scleroderma is characterized by a steady progression of cutaneous and systemic involvement, with remissions and exacerbations. In certain instances, especially in those patients with associated Raynaud's phenomenon, a regression or a remission is possible. In the late phase of the disease, other symptoms including restlessness, disorientation, convulsions, lethargy incontinence, and psychosis have been reported.

In general, most authors conclude that systemic scleroderma involves the mesenchyme and may occur wherever connective tissue normally exists and that the course of the disease is characterized by a progressive involvement, both in site and degree, of the skin and internal viscera which follows a generalized pattern. It is now recognized that involvement of the viscera may precede the symptoms of cutaneous manifestation.

Clinically it is generally accepted that the symptoms and *clinical findings in scleroderma are, in general, not diagnostic* but are dependent upon the specific site and the degree of involvement.

TREATMENT

There is no specific treatment for systemic scleroderma. A review of the literature during the past 5 years reveals that more than 50 specific methods of treatment have been reported, none of which has either been confirmed or has proved successful. These range from sleep therapy with opium and scopolamine to radical bilateral thoracic sympathectomy The evaluation of the treatment in scleroderma is difficult, as the course of this chronic disease is characterized by remissions and exacerbations, and, in the instance of acrosclerosis, even regressions may occur

At this time, steroid therapy offers the best prognosis, in that it may produce a remission or alleviate symptoms. While steroid therapy generally offers the best prognosis in the collagen diseases, scleroderma responds least.

Rodman [16] states that cortisone and corticotropin treatment

by some is believed capable of inducing a favorable response. Others are of the opinion that steroid therapy has arrested the progress of the disease, and still others feel that there is no fundamental alteration of the course of the illness. Most [17] note a quick return to pretreatment status when corticotropin or steroid is discontinued. To quote Leinwand in part, "There is no curative therapy. However, in a limited number of severe cases, cortisone appears to have arrested the progress of the disease. Salomon [18] states that, in his experience, improvement in skin manifestations was temporary and relapses occurred in all patients, 4 to 6 months after therapy had been terminated. No acute exacerbations of the disease occurred in those patients treated by him as a result of cortisone therapy.

Of the many surgical treatments reported, sympathectomy appears to be the most popular. Evans [19] recommends that patients with primary Raynaud's disease and mild secondary scleroderma of the hands with facial or yoke involvement receive sympathectomy of the first to the ninth thoracic segments. He further states that no drug therapy has been beneficial in his experience. However, most authors believe that sympathectomy is not to be recommended unless it is possible to produce vasodilatation and improved blood flow by temporary measures. Beigelman [20] concludes that sympathectomy gives only 5 to 6 months temporary relief.

The nonspecific treatment of systemic scleroderma consists of supportive care including general hygiene and nutrition, psychotherapy, occupational therapy, and physiotherapy. In those patients with acrosclerosis or associated Raynaud's disease, avoidance of cold is to be recommended. Physiotherapy and occupational therapy may prevent or be helpful in reducing the extent of the contractures resulting from atrophic changes of the skin and subcutaneous tissues. The prophylaxis and specific treatment of complications such as trophic ulcers, respiratory inhibition, calcinosis, and secondary infections are indicated.

Of greater importance, complete and periodic physical and laboratory examinations are required to determine the early existence of *visceral manifestations* so that early prophylaxis and

treatment may be initiated, for those specific organs or systems involved.

SUMMARY

Systemic scleroderma is a disease of the mesenchyme and may occur wherever connective tissue normally exists. The course of the disease follows a generalized clinical pattern with the joints involved first. The skin, the gastrointestinal tract and heart, the kidneys, and the lungs are further involved with progress of the disease. Characteristically the symptoms and clinical findings of visceral scleroderma are in general not pathognomonic but are dependent upon the tissue affected and the degree of involvement. Acrosclerosis or the presence of associated Raynaud's phenomenon offers a better prognosis, as in these patients spontaneous remission may occur and visceral manifestations occur to a lesser extent than in those patients without this clinical finding.

While there is no specific treatment, steroid therapy offers the greatest opportunity to aid these patients. However at its best it can offer only the possibility of alleviating symptoms or perhaps initiating a remission. Of the various collagen diseases, scleroderma responds least to steroid therapy It is most effective when utilized early and in rather high dosage.

Of the various surgical methods recommended, sympathectomy appears to offer the most successful results. However it is the opinion of most authors that this will only temporarily alleviate the vascular symptoms in those patients with associated Raynaud's phenomenon.

CONCLUSION

Until the cause of systemic scleroderma has been established and a specific treatment determined, the early diagnosis, nonspecific treatment, and prophylaxis of complications are of the utmost importance Periodic physical and laboratory examinations, including surgical pathological diagnosis, are required to determine the early existence of visceral manifestations, so that specific systemic prophylaxis and treatment may be initiated.

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DERMATOMYOSITIS

Dermatomyositis is a multiform disease comprising a nonsuppurative widespread myositis, variable cutaneous lesions and on occasion mucous membrane and visceral pathology. The onset may be acute and fulminant but more often is mild with low grade but progressive symptoms of muscular weakness and tenderness, facial and upper trunk edema, variable erythema, general malaise and weight loss. There are also a number of cases which have muscular weakness but no dermal involvement, or with only mild cutaneous thickening and hyperpigmentation. These cases have been termed chronic polymyositis.

CAUSE

The cause of this condition is entirely unknown. Until more is understood of the basic disease process, it is reasonable to continue to classify it among the connective tissue or diffuse collagen diseases, even though the principal pathologic feature is a more or less severe degeneration of the skeletal muscle fibers. To emphasize the overlapping elements in such a classification there are a number of reported cases that at one time or another have shown features of dermatomyositis, rheumatoid arthritis, lupus erythematosus, and scleroderma.

COURSE

Dermatomyositis is not a rare malady As an increasing awareness of the varied symptomatology has developed, cases with and without cutaneous manifestations have been observed in con siderable numbers. In one report from a general hospital acute dermatomyositis has been ranked second in incidence to systemic lupus erythematosus among the unusual collagen diseases. It is the most common of the unusual connective tissue diseases of childhood. It affects persons of any age including infants and the elderly The peak incidence is in the fourth and fifth decades with a slight predominance in women. The course of dermatomyositis is unpredictable and usually more severe in children than in adults. On occasion only a few muscle groups may be involved and recovery can be quite complete. On the other hand there may be a progressive and fulminating decline with death within a few months, weeks, or even days after appearance of symptoms. Involvement of respiratory and bulbar musculature has traditionally been considered to be a preterminal sign, however we have recently seen two persons with such involvement recover one partially and one completely following vigorous adrenal steroid therapy What the future of these individuals will be is uncertain. They are being continued on adrenal steroids. As a rule the disease runs a chronic fluctuating course, hence conclusions as to the value of short term therapy can be only tentative.

PROGNOSIS

The mortality rate is high. More than 50 per cent of persons affected with the acute variety die within a few months of onset of clinical symptomatology Death in these cases is due to progressive weakening of the respiratory and other bulbar musculature with accompanying aspiration or stasis *pneumonitis* and often a terminal septicemia. Among the remainder a few have a short benign illness with near complete recovery; a number of others continue to show low grade progression of symptoms and reach a plateau *in 3 to 7 years. In this static* state there is almost always some residual crippling with contractures and on occasion

calcinosis of a few or many muscle groups. There is a small but significant number of cases in which almost complete recovery of muscle strength ensues after severe acute myositis. These cases appear to be more prevalent since the advent of adrenal steroid therapy

CLINICAL PICTURE

The frequent and occasional general signs and symptoms of this polymorphic disease process are recorded in Table 4 1 Invariably there is a progressive loss of muscular strength due to a primary degeneration of the muscle fibers of a few or many muscles or even on occasion of the entire skeletal musculature. The muscles initially affected in most cases are those of the proximal limb girdles and of the anterior neck, so that movements of the hips thighs, shoulders, and upper arms as well as the neck flexors become progressively weakened and often tender Muscular weakness, pain, and tenderness vary considerably depending upon the location and extent of the pathologic process. There is no direct correlation between the presence of muscle fiber degeneration and the degree of muscular pain, hence in some cases with widespread involvement muscle pain and tenderness may be entirely absent. Listed in Table 4 2 are the general symptoms due to muscular involvement.

Table 4-1 GENERAL SYMPTOMATOLOGY IN DERMATOMYOSITIS

Common Symptoms	*Occasional Signs and Symptoms*
Malaise	Arthralgia or arthritis
Weight Loss	Raynaud' syndrome
Fever low grade	Visual defects, retinal pathology ocular palsies
Tachycardia	Buccal mucosa lesions
Rapid onset (25 per cent)	Sensory disturbances
Insidious onset (75 per cent)	

Table 4-2 MUSCULAR SYMPTOMS IN DERMATOMYOSITIS

Weakness, symmetrical, proximal girdle muscles affected initially
Pain on motion or at rest.
Tenderness, induration, and stiffness.
Atrophy often with contractures later
Dyspnea, dysphagia, and dysphonia due t specifi muscle involvement.
Any or all muscle groups may be involved.

The dermal manifestations are variable and not easily described. On occasion they are difficult to distinguish from the cutaneous features of lupus erythematosus or scleroderma. Characteristically in the early stage there is significant edema of the face and frequently also in a shawl distribution on the neck, upper chest, and arms proximal to the elbows. Accompanying this is erythema, often described as heliotrope (lilac) in color of the face, anterior chest, and shoulders or occasionally restricted to one of these areas alone. The upper eyelids are the most frequent location for such an eruption. Erythematous or atrophic lesions are often present over the bony prominences of the fingers, elbows, knees, and ankles. Chronic or low grade skin changes include areas of pigmentation and depigmentation, scleroderma like thickening, and reticulated telangiectasia. Listed in Table 4-3 are the various cutaneous signs that may be observed.

Table 4-3 CUTANEOUS MANIFESTATIONS IN DERMATOMYOSITIS

- Edema, especially eyelids, face, neck and shoulders
- Dusky lilac (heliotrope) erythema of eyelids, face, neck, elbows, and knuckles of hands
- Atrophic plaques over extensor joint surfaces
- Calcinosis, late
- Diffuse alopecia of scalp
- Miscellaneous
  - Erythema multiforme
  - Urticaria
  - Purpura
  - Lichenoid eruption
  - Bullous eruption
  - Hypertrichiasis

ASSOCIATION WITH MALIGNANCY

Of significant interest in recent years is the observation that a number of cases of dermatomyositis in adults have been associated with visceral malignant disease of variable type and origin. No such association has been reported in childhood. Dowling has summarized 30 cases of dermatomyositis with accompanying malignant tumor and concludes that the incidence of malignant disease in these persons is five times that expected in a comparably aged normal population. In the 30 cases carcinoma origi

nated eight times in the female sex organs, six times in the stomach, four in the breast, three in the lung, and once or twice each in several miscellaneous sites. The usual order of events in this series was initially the appearance of carcinoma followed later by the muscular disease The reverse was true on occasion, however Death in these cases was, on the other hand, almost always due to the myositis rather than the malignancy There has been considerable debate [4] concerning the effect of radical or suppressive therapy of the malignant tumor on the status of the associated dermatomyositis. Some authors have reported satisfactory regression of muscular symptoms, whereas others have not observed any change. Until this point is settled, it appears that a thorough search for a hidden malignant tumor should be conducted in every adult case of dermatomyositis, and if one is found, the most effective therapy should be applied promptly

PATHOLOGY AND LABORATORY FEATURES

The primary gross feature of all types of myositis, acute and chronic, is a change in color of the affected muscles from the normal red brown. Depending upon the amount of accompanying edema, muscle fiber destruction, and fibrosis, the muscles may vary from red or pink-gray to yellow white The principal microscopic pathologic feature is a widespread degeneration of striated muscle fibers. Fibers in all stages of destruction may be found (Figs. 4 1 4-2) and depending upon the intensity of the process there may be many or few fibers undergoing acute degeneration in any one muscle. Phagocytosis of necrotic muscle debris is common (Fig. 4 1) Some evidence of regeneration of muscle fibers is frequently present, but many of these efforts appear to be abortive. Diffuse or focal interstitial and perivascular cellular infiltrates of lymphocytes, plasma cells, histocytes, and occasionally neutrophilic or eosinophilic leukocytes are fairly constant findings.

The pathologic picture in the skin is as variable microscopically as it is clinically Some areas of involvement may be indistinguishable from scleroderma, showing dystrophic keratosis, moderate follicular plugging, and alteration of collagen tissue. More fre-

quently the superficial dermal layers are normal, but there are changes in the subcutaneous tissue (Fig. 4-3) which consist of edema, foci of hemorrhage, localized areas of collagen and fat necrosis, fibrosis, leukocyte invasion, and perivascular cellular



Fig. 4-1 Anterior thigh muscle from thirty-nine-year-old woman with subacute dermatomyositis. Two muscle fibers in the section have undergone degeneration, and their sarcoplasmic remnants are being removed by macrophage cells (×310).

infiltrations. These changes are not specific, but when found in the deeper dermal layers and the subcutaneous tissue, especially in combination with a myositis, the diagnosis can no longer be in doubt.

In any questionable case that manifests some muscular weakness, a muscle biopsy should be taken. A good deal of information can be obtained from a study of muscle tissue, and in recent years we have uncovered a number of cases of chronic poly



Fig. 4-2. Deltoid muscle biopsy from fifty-four-year-old man with acute dermatomyositis. Note hyaline, vacuolar and fragmentation types of degeneration in many of the muscle fibers in the section (×130)

myositis that had previously been given a variety of diagnostic labels. The site of biopsy should be selected carefully. It should be from a muscle that is obviously weakened, tender or indurated, but not from one that is severely atrophied. In acute dermatomyositis one of the shoulder girdle muscles (deltoid, trapezius, pectoral) or the sternocleidomastoid are most likely to

yield valuable information. A piece of skin should be taken at the same time.

Until recently there has been no clinical laboratory test of value in this disease Quantitative urine creatine and creatinine



Fig. 4-3. Skin biopsy from right shoulder of fifty-four-year-old man with acute dermatomyositis and edematous indurated skin of the neck, shoulders, and upper arms. Section of subcutaneous region shows mild interstitial edema, with foci of extreme edema, collagen necrosis, hemorrhage and acute inflammatory reaction (×30).

on occasion provide some helpful clues, but their levels depend upon so many variables that they are just as often misleading. The enzyme transaminase (glutamic oxalacetic transaminase) is normally present in high concentration in striated muscle tissue but in only very small amounts in the serum. Within the past year it has been noted that the serum level of this enzyme is invariably elevated in the acute case of dermatomyositis and often above normal in the more chronic one. Tabulated in Table

4 4 are several laboratory procedures of proven, questionable and possible value as aids to diagnosis in dermatomyositis

Table 4-4 LABORATORY DATA OF VALUE IN DERMATOMYOSITIS

Elevation of serum transaminase
Elevated urinary creatine, inconstant
Reduced urinary creatine, inconstant
Elevated sedimentation rate
Pathologic alterations in muscle and skin biopsy material
Characteristic electromyographi pattern
X ray evidence of soft tissue calcification (in late stages only)

DIFFERENTIAL DIAGNOSIS

Early in the course of the disease the true nature of the condi tion is rarely apparent. In our experience the most frequent initial diagnosis have been lupus erythematosus acute rheumatoid arthritis, myasthenia gravis, trichinosis, and scleroderma. Listed in Tables 4-5 and 4-6 are the various disorders which can be clinically simulated prior to and after the development of a skin eruption.

Table 4-5 DIFFERENTIAL DIAGNOSIS OF ACUTE DERMATOMYOSITIS PRIOR TO APPEARANCE OF CUTANEOUS MANIFESTATIONS

Poliomyelitis	Acute rheumatoid arthritis
Myasthenia gravis	Acut rheumatic fever
Muscular dystrophy	Acute nephritis
Polyarteritis nodosa	Polyneuritis
Systemic lupus erythematosus	Trichinosis
Thyrotoxic myopathy	

Table 4-6 DIFFERENTIAL DIAGNOSIS OF ACUTE DERMATOMYOSITIS WITH CUTANEOUS MANIFESTATIONS

Systemic lupus erythematosus	Trichinosis
Scleroderma	Erythema Solare
Porphyria	Avitaminosis (pellegra, scurvy)
Erysipelas	Acrodynia
Scleredema	Erythema multiforme

TREATMENT

The response to therapy in this condition is difficult to assess, because in many cases there is apparently a natural tendency to

repeated remissions and relapses More correctly these may be interpreted as clinical fluctuations. The great variety of therapeutic agents that have been tried attests to the fact that none has had any consistent measure of success. Various remedies which have been used and found to be of no value include testosterone, vitamin E, thyroid extract, para-aminobenzoic acid, and various antibiotics.

The aim of treatment in dermatomyositis should be control of the skeletal muscle and visceral degeneration, since it is progressive affection of these systems that gives the high mortality The dermal lesions are of incidental occurrence and usually subside if the remainder of the systemic disease can be brought under control.

There is no general agreement in the literature as to the value of cortisone hydrocortisone, prednisone, and ACTH in this condition. However it does appear that there is a somewhat greater incidence of improvement in cases adequately treated with the adrenal steroids. In the UCLA Medical Center in the past 3 years a number of cases have been treated with prednisone, the steroid of choice in my opinion. A fixed dosage schedule cannot be adopted, but in general in an adult an initial trial of 50 to 60 mg daily in divided doses seems to be necessary A larger amount may be needed if full pharmacodynamic effect is not manifested after 2 or 3 weeks. A minimum trial period of 2 to 3 months should be given. If a clinical response is noted during this period, a careful reduction in the dosage in decrements of 5 mg at weekly or bimonthly intervals can be undertaken. It appears that reduction below 15 to 20 mg daily within the first year is inadvisable, since a relapse has been observed in several patients when the dosage was brought below this level. Perhaps indefinite or at least very prolonged therapy with prednisone is indicated if improvement is observed. We have used weekly serum transaminase levels to monitor the patient's response to the adrenal steroids and have the impression that improvement, as measured by a drop in enzyme level, can be detected 2 to 4 weeks before there is definite evidence of clinical remission. Likewise in one case that began to relapse as prednisone was decreased below 15 mg

daily the serum enzyme level rose 10 days before evidence of recurrent muscular weakness could be detected with certainty

In all cases a thorough search should be made for a malignant tumor On occasion, however the severity of the patient's condition may preclude any detailed investigative procedures. A malignant tumor should be treated actively with resection, irradiation, or other measures, even if it is quite certain that all tumor tissue cannot be removed, since some authors have reported recession of the myositis after partial as well as total tumor eradication. As mentioned before, there continues to be some debate about the actual value if any of tumor removal on the associated muscular disease.

A number of general measures should be used along with steroids as indicated in each case. For severe involvement of respiratory musculature a tracheotomy oxygen, and a mechanical respirator may be lifesaving. Intravenous or gastric tube feedings are necessary on occasion to circumvent severe prostration and pharyngeal and esophageal muscle weakness. Sedatives and opiates may be needed if restlessness and muscular pain are intense. Particular attention should be given to respiratory excursion volume when the patient has been given an opiate Prophylactic antibiotic treatment, in the acute stages, should be administered to avoid inhalation or stasis pneumonitis and other infection. A broad spectrum antibiotic is advisable in this situation.

Physical therapy has value in any stage of the disease, but especially in the chronic or recovery phases. In acute disease correct positioning of limbs may prevent subsequent deformity and hot packs may ease the muscle pain to some extent. In the chronic stages development of contractures can be combatted with massage, gentle manipulations, and exercises as well as with orthopedic devices. In the recovery phase carefully graded exercises can encourage return of a variable degree of muscle strength and bulk. Occasionally such a recovery is surprisingly complete, especially so when one views the extent of muscle fiber destruction as seen in biopsy specimens in the acute stages of the disease

In general it appears that when acute dermatomyositis is brought under adequate adrenal steroid therapy early in the

course of the disease there is a fairly satisfactory opportunity to induce a remission or even an apparent cure of the morbid state. In the more insidious chronic polymyositis with muscular atrophy fibrosis and contracture prednisone rarely appears to be of value, and symptomatic general management is all that can be recommended.

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Rudolf L. Baer

5

POLYMORPHOUS LIGHT ERUPTIONS

THE SKIN OF HUMAN BEINGS has the capacity to respond in various definite ways to exposure to sunlight. For example in small doses sunlight causes pigmentation as well as thickening of the horny layer. In larger doses it causes the well-known sunburn reaction.

In addition to these physiologic responses the reactivity of the skin to sunlight can be deliberately increased by topical application, injection, or ingestion via the photodynamic action of so-called photosensitizers. The photosensitizer absorbs radiant energy of a specific wavelength or spectral range and, rather than being altered itself by the energy, transmits the absorbed energy to adjoining molecules in the skin and causes them to be changed chemically. For example, crude coal tar is a well known photosensitizing agent. If a patient, after having applied a crude-coal-tar-containing preparation, exposes himself to sunlight, he is likely to develop a severe burn from an exposure so small that under ordinary circumstances it would not cause even the slightest visible reaction on his skin. Systemically the same photodynamic process can be initiated by injecting eosin or certain porphyrins and other substances.

This discussion will not deal with physiologic cutaneous responses to small or large doses of sunlight, or with the skin's response while under the influence of known photodynamic agents, but will deal with a group of eruptions precipitated or caused by exposure to sunlight as well as light from artificial sources, which are now usually classified under the name *polymorphous light eruptions*. The name *chronic polymorphous light eruptions* was first suggested by Hausmann and Haxthausen in 1928, who distinguished two main types: the papular and the eczematous type. They stressed the preponderance of women and of blond persons among those affected. Since that time different authors have extended the meaning of the term beyond that given it by its original authors.

Polymorphous light eruption is a clinical concept, and since information with respect to its cause and mechanism is very deficient, the term cannot be used to denote a causal entity. The term *polymorphous light eruption* as used by me refers to a group of eruptions which are characterized by papules, papulo-urticarial lesions, urticas, vesicles, erythemas, and plaques, and various combinations of these. I shall exclude any eruptions which can be fitted into the porphyrias or which belong to clinically well defined entities in which light is only a secondary rather than the apparent primary causal factor, such as, for example, lupus erythematosus and some cases of seborrheic dermatitis and rosacea. As the word *polymorphous* implies, these eruptions are characterized by a variety of lesions rather than by one particular type of lesion as in solar urticaria, a monomorphous dermatosis, where all the lesions are wheals. It should be noted, however, that one or two types of lesions often predominate in the clinical picture of polymorphous light eruption.

Since the cause of polymorphous light eruptions is unknown, it is not possible to categorize them on the basis of their underlying mechanisms. In view of this it is still necessary to group them according to their principal morphologic features.

MORPHOLOGIC CLASSIFICATION

The classification used here comes from the work of Lamb in a very large group of patients. According to him the largest group of patients with polymorphous light eruptions, comprising about 75 per cent of cases, present plaque-like lesions. The plaques are 2 to 5 cm in diameter and often involve the cheeks, preauricular

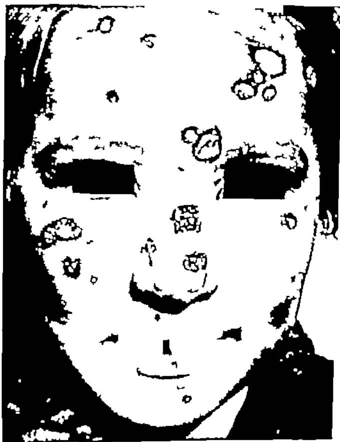


Fig. 5-1. Polymorphous light eruptions. Crusted vesicular lesions in girl aged six. Whitish color is caused by medicaments. (*Courtesy of Department of Dermatology and Syphilology and Skin and Cancer Unit, New York University—Bellevue Medical Center.*)

areas, the V and the posterior parts of the sides of the neck. They are pinkish red, lichenified, thickened, and scaly frequently show telangiectases, and may be combined with, and often perhaps are secondary to prurigo-like papular and vesicular lesions.

In the next largest group of polymorphous light eruptions, comprising about 15 per cent of the cases according to Lamb [14] prurigo-like papular and vesicular lesions predominate (Fig. 5 1)



Fig. 5-2. Same patient as Fig. 5-1 Scars on forehead remaining after healing of lesions (Courtesy of Department of Dermatology and Syphilology and Skin and Cancer Unit New York University—Bellevue Medical Center.)

Plaque-like and urticarial features may be admixed. The vesicular lesions may become crusted, and may ulcerate and leave scarring and atrophy (Fig. 5-2) The conditions formerly classified as summer prurigo, hydroa aestivalis, prurigo aestivalis and perhaps also hydroa vacciniforme belong to this group.

The third group is made up of the eczematous (papulovesicu lar erythematous) eruptions. These eruptions formerly were often called eczema solare and sometimes are misdiagnosed as

contact dermatitis, which they resemble clinically. They may become lichenified and excoriated and they can diffusely involve the entire sunlight-exposed area or affect only limited areas on the cheeks, chin and neck.



Fig. 5-3. Polymorphous light eruptions. Edematous sharply defined lesions in boy aged one. (*Courtesy of Department of Dermatology and Syphilology, and Skin and Cancer Unit, New York University—Bellevue Medical Center.*)

The fourth and smallest group encompasses erythema multiforme-like eruptions and persistent erythemas (Figs. 5-3, 5-4). The lesions may be maculopapular and erythematous with distribution over the nose, malar areas, and neck. These are the eruptions which in the past were often referred to as erythema perstans solare and which at times are quite reminiscent of the acute or subacute form of lupus erythematosus. As a matter of fact Cahn et al. [3] considered the possibility that this type of polymorphous light eruption might in some cases be a manifestation of systemic lupus erythematosus.

It is evident from these descriptions that there is no sharp delineation separating the various types of polymorphous light eruptions. The diagnosis is made usually on the basis of the clinical picture plus a history indicating that the eruption exacerbates



Fig. 8-4. Polymorphous light eruptions. Erythematous papular and nodular lesions in woman aged twenty-nine. (Courtesy of Department of Dermatology and Syphilology and Skin and Cancer Unit, New York University—Bellevue Medical Center.)

during periods when there is exposure to sunlight and undergoes remissions at times when there is little or no opportunity for such exposures. One must also remember that polymorphous light eruptions can be due to light from other sources, such as fluorescent lights. Light eruptions which at first are seasonal in character may, when they recur year after year, gradually become perennial. Under such circumstances one is likely to overlook the fact that at the start there was a definite relationship to exposure to sunlight unless the history is very carefully taken.

Polymorphous light eruptions can begin or recur within a few hours after exposure to the causal radiation but more often start gradually and insidiously. It has been suggested that the onset of the eruption is more dependent on increases in the intensity of radiation rather than an absolute intensity. Generally it seems that the more acute the type of eruption (e.g., eczematous, maculo-urticarial, erythematous), the more likely is a recurrence

after a single exposure, and the more chronic the type of eruption (e.g. lichenified, plaque-like) the more likely is a recurrence only after repeated exposures.

DISTRIBUTION

Allington has given an excellent description of the areas of predilection for polymorphous light eruptions. On the hands the dorsa are affected, but the opposing sides of the fingers, the webs, and the distal phalanges may be spared. The radial and lateral aspects of the wrists and forearms are likely to be affected, while the volar and ulnar aspects are free. On the arms the eruption will be found on the lateral aspects, especially those parts not protected by the shirt sleeves, and on the face, principally on the lower portion of the forehead and on the nose and cheeks. Other landmarks of involvement may be small areas of the upper eyelids, the rims, lobes, and exposed portions of the pinna of the ears, the front and sides of the chin and the exposed mucosal surface of the lip. On the neck one should look for the lesions in the V area and on the sides and back. Areas which are often spared are those close to the hairline, the eyelids, the recessed portions of the ears, the retroauricular areas, the upper lip beneath the nose, the mucosal surface of the upper lip, the transverse sulcus of the chin, and the submental region.

Patients who drive automobiles may present a much more pronounced eruption on the left side, where there is greater opportunity for exposure to light, than on the right side, which is usually protected against sunlight by the roof and side of the car.

TESTING PROCEDURES

Testing for light sensitivity is desirable or essential for a number of reasons. True, in many patients the clinical picture together with a good history will suffice to establish the diagnosis of polymorphous light eruption. In doubtful cases, however, deliberate exposure to sunlight or other suitable source of light under appropriate conditions may be helpful in establishing or ruling out the diagnosis of polymorphous light eruption. But even when

there is no doubt of the diagnosis, it is often desirable to carry out tests in order to identify the offending spectral range. A very practical reason is that unless one knows to what part of the light spectrum the patient is hypersensitive, it is difficult to advise him on how to protect himself to best advantage. There are also important theoretical and scientific reasons for performing such tests Only if one knows the spectral range involved in these cases will it be possible eventually to ascertain which substances in the skin or which of its components absorb the pertinent wavelengths and mediate the light sensitivity This knowledge is essential if we are to advance in our understanding of the causal mechanisms responsible for producing these eruptions.

To carry out such tests one must have a source of light which emits the offending rays in sufficient quantity to be capable of eliciting a clinical reaction in sensitive skin. Moreover it is desirable that the intensity of emission be the same at all times. The situation here is comparable to that in patch testing in allergic eczematous contact dermatitis, where even in highly sensitive subjects a reaction will occur only if the allergen is present in adequate concentration and is left in contact with the skin for a sufficiently long period of time.

Among the sources of radiation for testing in polymorphous light eruptions, natural sunlight obviously in many ways is ideal. It is notoriously difficult, however to rely on sunlight as a source of light for skin testing, since in many localities it is available only during some parts of the year and even then irregularly Furthermore, its intensity varies greatly in different places at the same time and in the same places at the same time and in the same place at different times of the year and hours of the day Sunlight reaching the skin on a hazy day may be relatively rich in ultraviolet rays and poor in visible and infrared rays. Winter sunlight, which passes more diagonally through the ozone-containing layer in the earth s atmosphere than summer sunlight, is relatively poorer in the short ultraviolet rays than in long ultraviolet and infrared rays.

The most readily a ailable artificial light source usually is the hot quartz mercury vapor arc lamp. Its emission of light waves,

however occurs in isolated wavebands and not as a continuous spectrum. Furthermore, the hot quartz mercury vapor arc lamp emits ultraviolet rays shorter than 2,800 A, which are not contained in natural sunlight reaching the earth's surface. These very marked differences in the quantity of energy emitted at various spectral segments often make it difficult to carry out tests with such lamps Generally about one-fourth of the radiation of such lamps is in the ultraviolet range another one-fourth in the visible light range, and one-half in the infrared range.

The cold quartz mercury vapor lamp has its most intense emission in that segment of very short ultraviolet rays which is not present in sunlight reaching the earth's surface. This makes the lamp clinically useful to produce peeling, but makes it useless for testing in polymorphous light eruptions

Carbon arc lamps are no longer generally available. In some ways they are most suitable for testing in polymorphous light eruptions, provided of course that the appropriate carbons are used. However the output of the arc is liable to vary considerably so that one cannot be sure of the intensity of the radiation administered to the test area.

Whatever the source of radiation may be, it is necessary to separate the various spectral ranges in order to identify the wavelength or range of wavelengths involved in the production of polymorphous light eruptions. Monochromatic light would be ideal for this purpose, but apparatus emitting light of one particular wavelength in a sufficient quantity for skin testing is practically unobtainable in most places. Therefore, one must rely on separating the various wavebands by means of filters which are interposed between the source of light and the skin Window glass, a simple filter available to everyone, does not allow transmission of wavelengths of less than 3,200 A and thus filters out the sunburn part of the short ultraviolet spectrum. For more detailed studies, colored glass filters can be utilized. Another type of filter the so-called interference filter to my knowledge has not been widely used in this country for medical purposes

Tests for light sensitivity should be done on small skin areas, with careful shielding not only of the surrounding skin but of the

entire body. A considerable amount of radiation will penetrate linen or cotton sheeting or curtain material of the type often used in hospitals to separate cubicles or beds. Unless shielding is perfect, patients with marked hypersensitivity to light may undergo severe, widespread, and even dangerous reaction. Caution should also be taken with respect to the dosage of radiation given. In polymorphous light eruptions one erythema dose may be given as a first exposure. If no unusual reaction ensues within 3 days, several erythema doses can be given at one time if one wants to reproduce the lesions.

Only in a minority of patients can polymorphous light eruption be deliberately reproduced or can an abnormal reaction to light be demonstrated through skin testing of previously unaffected areas with artificial sources of light. The previously mentioned deficiencies of the light sources are one of the reasons for the frequent failure of such tests. Probably also a succession of adequate exposures is sometimes required to bring about the characteristic cutaneous changes. Moreover, as Lamb has pointed out [14], polymorphous light eruptions tend to locate in areas where more or less permanent changes have already occurred in the cutaneous tissues due to exposure to large quantities of sunlight over many years. Tests might well prove negative when they are done in sites which have not been subject to such preceding damage. Of course this difficulty can be circumvented if one tests previously involved areas of skin.

The test reaction consists of papular, papulo-urticarial, or eczematous changes. Levy et al. [20] also have described an intense persistent erythematous reaction. The latter probably corresponds to the clinical condition described as erythema perstans solare.

DIFFERENTIAL DIAGNOSIS

As far as the clinical diagnosis is concerned, one should always consider the possibility of a polymorphous light eruption when only the sunlight-exposed areas are involved, but in each instance other possible diagnoses should be ruled out. This includes all those eruptions which may exclusively or principally involve the

exposed areas of the skin as well as dermatoses which are precipitated or aggravated by exposure to sunlight. Allergic eczematous contact dermatitis, especially when it is caused by airborne allergens, may be limited entirely to these exposed areas. An isomorph reaction (Koebner's phenomenon) elicited by sunlight may cause certain other common dermatoses (e.g., psoriasis, lichen planus, rosacea, seborrheic dermatitis) to affect only those areas which are exposed to sunlight.

The chronic discoid form of lupus erythematosus must be differentiated especially from the plaque like eruptions. Chronic discoid lupus erythematosus is more likely to involve the center of the face, the lips, mouth, and scalp. It shows more tendency to plugging and dilatation of follicles and tends to heal with atrophy. The subacute and acute forms of lupus erythematosus must be differentiated from the more acute forms of polymorphous light eruption. At times this may be very difficult. In polymorphous light eruption the patient's general condition is good, while patients with acute and subacute lupus erythematosus usually show evidence of systemic involvement.

Drug eruptions and contact dermatitis may be associated with photosensitization and involve only the exposed areas. This accounts for the involvement of the light-exposed areas in drug eruptions due to sulfonamides and Thorazine. Photosensitivity also is often a factor in allergic contact dermatitis due to topical Phenergan preparations and explains at least in part the very pronounced involvement of the light-exposed regions.

The bullous, papulovesicular eczemalike changes of porphyria may in some cases give rise to confusion with polymorphous light eruptions. Examination for porphyrins and for the physical and other changes characteristic of porphyria should be helpful in making a differential diagnosis in doubtful cases.

Urticaria solare, erythema exudativum multiforme, and pellagra are among the other differential diagnostic possibilities which may have to be considered.

MECHANISMS

Our present knowledge regarding the underlying mechanisms in polymorphous light eruptions is unfortunately extremely limited. In most cases in which it is possible to ascertain the offending segment of the light spectrum the sunburn part of the ultraviolet spectrum was found to be involved. In others it was the blue-violet part, and in still others it was any type of radiation capable of causing an intense erythema. The very essential information as to what particular substances in the skin mediate the reaction by absorbing the causal wavelengths is still lacking. An association of polymorphous light eruption with certain bacterial or viral infections has been repeatedly stressed in the literature. The possibility has been considered that a deficiency in gonadotropic hormone may play a role, and successful treatment based on its correction has been reported. A disturbance in liver function also has been repeatedly suggested, but the available evidence is inconclusive. Disturbances in hormonal and hepatic function in turn might lead to deficiencies in protein, vitamin, and mineral metabolism, which also have been claimed to play a causal role in hypersensitivity.

Many authors favor the concept of an allergic mechanism, and there is much evidence to support this. Perhaps patients suffering from these eruptions have developed an allergic sensitization to a normal or an abnormal metabolite which is formed or released upon exposure of the skin to certain wavelengths of light. Actually passive transfer antibodies to light have been demonstrated in blood serums of only a small percentage of patients with polymorphous light sensitivity but this fact in itself does not necessarily militate against the possibility of an allergic mechanism. Phases of increased and decreased sensitivity to light suggesting but by no means proving an immunologic mechanism have been observed. Moreover exposures of a small skin area to the offending part of the light spectrum have caused flare-ups of distant unexposed sites which previously had been affected by polymorphous light eruption. S. Epstein and others [5] also have shown that true photoallergic sensitizations to certain drugs not only

occur under natural conditions but can be deliberately induced in some subjects While it appears certain that some cases of polymorphous light eruption are based on an allergic mechanism, existing proof to support the hypothesis that all cases are allergic in nature still must be deemed inadequate.

There remains a possibility that polymorphous light eruption might be caused by as yet undiscovered photodynamic substances These might be acquired either by ingestion, inhalation, or contact, or they might be the result of endogenous production of a photosensitizer due to an error in metabolism. No such substance has been demonstrated in the blood, stool, or urine of affected patients, but it is conceivable that endogenous production of such a substance could take place in the skin itself without spilling over into the blood stream, stool, or urine. Immediately after exposure to light some investigators have been able regularly to extract substances which absorb radiation between 4,800 and 5,200 A from the urine of patients with polymorphous light eruptions. *In this connection it is well to be aware of the fact that* the manner in which photosensitizing substances sometimes exert their effects is more complicated than one would ordinarily imagine For example Grzybowski [8] reported that ingestion of Chenopodium, a herb which is also called goosefoot or pigweed, caused photosensitization in women in Poland during World War II only when they were suffering from malnutrition The same herb could be eaten with impunity in the absence of malnutrition. Finally the possibility of a genetic factor cannot be ruled out *entirely since familial occurrence of polymorphous* light eruptions has been reported.

TREATMENT

The ideal treatment of polymorphous light eruptions is complete avoidance of exposure to the sun or other sources of light causing the eruption. In general however this theoretical goal cannot be achieved under the prevailing practical conditions. Even so it is not only desirable but imperative that every patient be instructed to avoid such exposures to the utmost feasible extent. In some forms of hypersensitivity to light gratifying results

have been achieved by keeping patients in a completely darkened room for one or more weeks, and perhaps this procedure would be effective also in polymorphous light eruptions. Patients should be told that light coming from an overcast sky and light reflected from the sea, sand, light walls, or from other very light surfaces, may contain large quantities of radiation which can maintain the eruption or cause recurrences. When fluorescent lamps or other artificial sources of light emit the harmful rays, these lamps usually can be replaced or shielded in such a way as to protect the patient.

Wide-brimmed hats and closely woven wearing apparel including long sleeves and gloves, covering as much as possible of the skin's surface, are among the protective devices which can be employed. When the sensitivity is to the sunburn part of the spectrum, window glass should be interposed in so far as possible between the light source and the skin. For example, while driving a car the windows should always be closed on the sunny side.

Ointments, pastes, and creams, if applied in sufficiently heavy layer, will shield the skin on a purely physical basis against a wide range of ultraviolet and visible radiation. Paste of zinc oxide and petrolatum have been used successfully for this purpose, but for most people consistent use of heavy layers of these messy preparations is not feasible.

The protective effects of topically applied preparations can be substantially increased by the incorporation of so-called chemical sunlight filters, i.e., substances which selectively absorb the offending wavelengths. *For those with polymorphous light eruptions* due to the sunburn part of the spectrum tannic acid 2 to 4% is still the single best chemical filter. However, because of the staining properties of tannic acid, colorless substances such as *p*-aminobenzoic acid 10 to 15% or its esters, menthyl anthralinate 10%, digalloyl trioleate 3%, to mention only those in common use in commercial preparations at the present time, are preferable. Commercial preparations containing suitable chemical filters for persons with sensitivity in the longer ultraviolet and visible light are not available, but an ointment containing 50,000 I.U. of beta carotene per gram of base has been suggested.

Unless the prescribing physician is aware of the factors which determine the efficacy of such protective topical preparations, he may impart a false sense of security to those of his patients who use them. The best sun filter will give poor protection when applied to the skin in a very thin layer. Obviously the heavier the layer of chemical filter and vehicle, the greater the amount of radiant energy which can be absorbed. Certain vehicles—for example, water or alcohol—deposit only a rather thin layer of the sun filter. Moreover liquid preparations which contain the chemical sun filter in water or alcohol and certain other vehicles are liable to wash away as soon as the patient bathes, swims, showers, or perspires heavily. Under these circumstances their protective effect is quickly lost.

Systemic administration of a nontoxic and nonallergenic agent which is capable of absorbing the damaging wavelengths of light after deposition in the horny layer of the skin would be an ideal solution to the problem of polymorphous light sensitivity. The beneficial effects of antimalarials such as Aralen, Atabrine, and Plaquenil in polymorphous and other light-sensitive eruptions at first were explained on the basis of such a deposition in the horny layer of the skin. Subsequent studies showed that this is not the principal mechanism of action of these drugs. Rather they appear to possess a peculiar antiinflammatory action, based on an as yet undiscovered mechanism. There seems to be no major difference in the efficacy of Aralen, Atabrine, and Plaquenil in suppressing polymorphous light eruptions, although at times one may prove superior to the others.

The recommended doses are 250 to 750 mg per day for Aralen, 100 to 300 mg per day for Atabrine, and 200 to 800 mg per day for Plaquenil. Aralen appears to be less likely to produce cutaneous, hematologic, or other side effects than Atabrine. Plaquenil has not yet been sufficiently widely used in polymorphous light sensitivities to permit conclusive comparisons of side effects.

Among other systemically administered medicaments which have been suggested for treatment of polymorphous light eruptions are Pyribenzamine and other antihistamines, 8-methoxypsoralen, sodium para-aminobenzoate, and certain gold salts. In

general these drugs appear to be either ineffective or at least not sufficiently effective to warrant a trial. Lamb et al. [14] gave chorionic gonadotropin (pregnant mare s serum) 500 I U daily or every other day for 1 to 3 years with a resulting cure in some of their patients. In males past fifty androgenic hormone was added. These authors stress that trials of this method for only 1 or 2 months are useless.

Meticorten and related compounds are indicated only for suppression of very acute exacerbations of polymorphous light eruptions, if the antimalarials fail to give speedy relief The corticosteroids are not indicated for routine continuous suppressive therapy in these cases.

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S William Becker

6

HYPERPIGMENTATION AND DEPIGMENTATION

THE NATURE OF melanin pigmentation, hyperpigmentation, and depigmentation are fairly well appreciated. Migrating globular cells, presumably from the neural crest, can be identified in the Negro embryo at the tenth week of intrauterine life [1]. They become dendritic in the fetus and locate in two layers, one adjacent to the epidermis and the other deeper in the dermis. In the present discussion, only the superficial layer is of interest, since pigmentary tumors, including blue nevi, are not considered. Epidermal melanocytes are seen as a syncytial sheet at the epidermodermal junction, with dendrites extending into the epidermis. They are dopa positive and, if the skin is treated by irradiation (ultraviolet, roentgen, or radium) are tyrosine positive. By chemical changes, starting with tyrosine, polymerization of indole 5,6-quinone produces melanin, which furnishes the skin with its brown pigment. Overactivity of the ferment (tyrosinase-dopa-oxidase) results in hyperpigmentation (melanosis) and decrease or failure of ferment activity causes partial or complete leukoderma. Increase or decrease of melanin-stimulating hormone (MSH) from the pituitary gland results in the same changes. If

melanin is increased in the epidermis only the color is brown, while considerable melanin in melanophages in the papillae and superficial dermis introduces a grayish hue, as seen in post inflammatory melanosis.

MELANOSIS

Melanotic hyperpigmentation is known as melanosis, which alteration is most readily recognized in patients with a high tanning potential. The color of the hair and/or irises does not always give a clue to the tanning power of the skin, which is the feature

Table 6-1 MELANOSIS

Prenatal

- Generalized
  - Racial
    - Lines of demarcation
  - Nonracial
- Localized
  - Lentigo profusa
  - Ephelides

Acquired

- Lentigo
- Lentigo senile
- Lentigo maligna
- Hormonal
- Physical
  - Electromagnetic irradiation
    - Ultraviolet irradiation
      - Solar melanosis
        - Direct
        - Indirect
        - Photosensitization
    - Roentgen rays
    - Radium rays
    - Thorium X
    - Isotopes
    - Infrared irradiation (heat)
      - Melanosis calorica
      - Burns (palmar)
  - Trauma (tattoo)
- Melanosis in internal medicine
- Central nervous system melanosis
- Postinflammatory melanosis
- Mucosal melanosis

in which we are especially interested. In any pigmentary report, the tanning potential of the skin should always be mentioned. Some varieties of melanosis are genetic (prenatal melanosis) Members of various races are pigmented in different degrees, varying from least in light-skinned Caucasions to most in dark skinned Negroes. Offspring from one parent of a dark and one of a light race tend to possess coloring of a shade between the two

PRENATAL MELANOSIS

Prenatal melanosis is relatively infrequent in Caucasians, compared with the acquired type. The generalized type is less common than the localized. Wende and Baukus [2] reported generalized melanosis in a girl who slowly became pigmented at the age of one year The pigment became lighter at the age of five years. Her brother also developed generalized hyperpigmentation at the age of one year Scheidt [3] reported 14 persons in four generations and Orth [4] reported 2 additional cases. Leber [5] reported 22 patients in 45 members of six generations. Inheritance was given as irregularly dominant.

In the localized variety Gertler [6] reported familial melanosis of the terminal phalanges. Other individuals with localized melanosis show an irregular pattern A child presented by me at the Chicago Dermatological Society in 1942 [7] first developed dark brown melanotic macules at the age of eight months. They slowly increased in number up to two years of age. On the genitalia, medial surface of the thighs, both axillae, posterior portion of the neck, dorsal aspect of both ankles, right hand, and fingers were dark brown, velvety macules up to several centimeters in diameter Microscopic study revealed melanosis of the basal epidermal layer with a few melanophages in the papillae and superficial dermis. The stratum corneum contained much pigment. The mother stated that the stratum corneum rubbed off with a towel after bathing was brown. There were no nevus cells, although the epidermal melanocytes seemed to be increased in number Another form of loc lized melanosis is lentigo profusa, which consists of uni- or bilaterally distributed closely set melanotic

macules, of varying shades of brown, located on any part of the body and, if about the mouth, sometimes on the oral mucosa. Microscopic examination reveals simple increased pigment activity in the basal layer of the epidermis. If treatment is desired, they may be bleached by Benoquin ointment.

Lines of Demarcation

Pigmentation in the darker races is not always uniform over the body but sometimes varies so abruptly as to form a definite line, with more pronounced pigmentation on one side than on the other. Such lines are called lines of demarcation. Futcher [8] called attention to a peculiarity of pigmentation of the arms of Negroes. The anterolateral surface of the upper arm was darker on the outer aspect than on the inner, with an abrupt nearly straight line 10 cm long. He observed 200 Negroes of both sexes from the age of eleven to seventy four years in a hospital ward for adults. A sharp, distinct line was seen in 17.5 per cent and was unilateral in 2.0 per cent. The incidence was the same in both sexes and at all ages. Biopsy showed the same amount of pigment on both sides of the line. The following case report is typical:

J. W., a male Negro, aged 28, with myasthenia gravis, had noted a vertical line on the anterior surface of both arms as long as he could remember. The skin was considerably darker laterally than medially (Fig. 6-1). Diagnosis was made of lines of demarcation. He also presented a unilateral lesion on the left side of the upper back in the pattern of lentigo profusa, with maculopapular lesions. Microscopic examination showed lentigo profusa, with no evidence of pigmented nevus.

Miura [9a, 9b] reported several demarcation lines with different degrees of pigmentation on each side in Japanese. Six areas of the arm and upper chest, one on the thigh, and one on the back were described. He discussed various theories of causation but believed that some of the lines coincided with the demarcation lines of the centripetal nerves.

Ephelides

Commonly known as freckles, ephelides are yellowish-brown or brown macules varying from punctate lesions to those a few

millimeters in diameter Siemens [10] stated that the depth of pigmentation varies inversely with their size. They are located on exposed surfaces, chiefly on the face (nose, forehead, temples, cheeks, upper lip, and chin) and the neck, which are exposed to

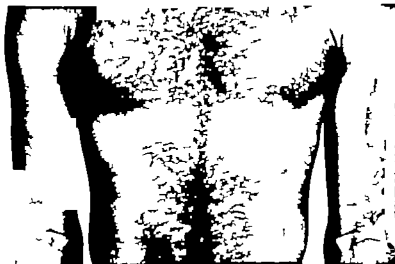


Fig. 6-1 Lines of demarcation in male Negro aged twenty-six. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

a certain amount of ultraviolet radiant energy from the sun. Other involved areas are the arms and upper part of the trunk, especially on the back, in persons who sunbathe. They are more frequent in light-complexioned individuals, sandy and auburn-haired persons. Prosser [11] stated that freckling seems to be due to a single dominant gene which is linked to that for red hair. Jankowsky [12] stated that red hair and freckles are seen together in the population of areas where races with fair and dark complexion intermingle because of mosaic inheritance.

Freckles appear in childhood, depending on the amount of ultraviolet irradiation to which the skin is exposed. Siemens [10] stated that one-quarter of the total number of freckles is present at three years of age, one-third at four years, and one-half at five

years. Matarasso [13] stated that they remain constant after twenty five years of age. They appear or become prominent in summer and disappear in the winter although they can be seen in the winter under ultraviolet irradiation (Wood's light) In very light-complexioned persons, the only cutaneous pigment may be in the freckles, while in slightly darker persons, there is lighter diffuse pigment between them. Some freckles, known as cold freckles, usually on the trunk, persist during the winter

The pigment in ephelides is melanin. Their presence seems to be due to irregular distribution of enzymatic activity The darkening of freckles has been shown by Folsher et al. [14] to be the result of direct melanosis by long wave ultraviolet radiant energy between 430 mm and 460 mm. They are also darkened by roentgen and similar rays and by systemic administration of MSH Cortisone and pregnenolone are also active, according to Brunner et al [15]

Treatment of freckles is carried out by mildly exfoliative preparations, of which 5 per cent ammoniated mercury ointment is an example. Winter [16] recommended 25 per cent phenol in ether for removal of freckles, although it causes pain and toxic symptoms may occur Monobenzyl ether of hydroquinone in 2 to 5 per cent strength in ointment, collodion, or adhesive plaster was recommended by Schwartz and Peck [17] Matarasso [13] recommended solid carbon dioxide, applied long enough to cause a depression that persists for 2 or 3 seconds More recently Kaminsky [18] and also Caver [19] reported that freezing with ethyl chloride as used preceding dermabrasion is followed by sufficient reaction to eliminate freckles permanently This would seem to be a method that should be given further trial

ACQUIRED MELANOSIS

Lentigo

Lentigo designates an acquired dark brown macule usually a few millimeters in diameter Identical lesions in infants and children ordinarily progress to form flat nevi, as studied by Stegmaier and Montgomery [20] Later in life, some lentigines remain as

such. They are seen on various parts of the body but are quite prominent on the vermilion border and on the dorsal surfaces of the hands. Microscopic section reveals increased melanoblastic activity with no neoplasia of cells as seen in nevi. On the backs



Fig. 6-2. Senile lentigo in woman aged sixty. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

of the hands and other parts of the body lentigines are seen beyond middle life. They are called senile lentigo by Cawley and Curtis [21] who state that they occur in 25 to [illegible] per cent of persons over fifty years of age. Miescher et al. [22] expressed the belief that senile lentigines are primitive seborrheic keratoses. The following case is illustrative of senile lentigo.

Mrs. M. B., aged 60, had had medium brown macules on the dorsum of the hands for several years (Fig. 6-2). Microscopic section showed melanosis of the basal layer of the epidermis, especially of the

inner extremities of the rete processes, which tended to be clubbed (Fig. 6-3)

This picture corresponds to that described by Cawley and Curtis. Treatment consists of application of Benoquin ointment



Fig. 6-3. Senile lentigo, same patient as in Fig. 6-2 (low power H&E stain) (Courtesy of Veterans Administration Hospital, Long Beach Calif.)

Senile lentigo must be differentiated from lentigo maligna, also seen more frequently beyond middle life as a variegated brown plaque, which eventuates in a tumorous melanoma. Biopsy is necessary for diagnosis and shows malignant neoplasia of melanocytes at the epidermodermal junction. Treatment consists of wide and deep surgical excision, with consideration of prophylactic regional lymph node removal

Hormonal

The most common hormonal melanosis is that of pregnancy The areas involved are the genitalia, the axillae, nipples and areola and linea nigra. Bloch and Guldberg [23] and Guldberg [24] showed that pigmentation of pregnancy could be produced by injection of estrogenic hormone and that, if applied locally to castrated male guinea pigs, a direct melanogenic action on the nipple and areola took place. Flerz [25] showed that local action of stilbestrol induced melanosis of the nipple and areola of castrated male guinea pigs, which was confirmed by Davis et al. [26] Utino [27] showed that melanophore hormone (probably identical to MSH) is excreted in the urine of pregnant women in small amounts at the beginning of pregnancy increases gradually then suddenly toward the end of pregnancy Melanosis of pregnancy recedes in part after delivery Addison s hypoadrenocortical melanosis is discussed later

Physical

The chief physical causes of melanosis are various electromagnetic irradiations, varying from gamma rays through infrared rays.

Solar One of the best known and most frequently observed of the melanoses is that caused by exposure to sunlight. It results from one or both of two mechanisms, known as direct and indirect. Direct pigmentation, according to Miescher [28] is caused by change of preformed oxygen-poor melanin into dark oxygen-rich melanin by long-wave ultraviolet irradiation between 300 mμ and 460 mμ. After exposure, the minimum latent period is a minutes and the maximum is up to 1½ hours. Microscopic section shows no inflammatory change. Henschke and Schulze [29] found that direct pigmentation is especially strong from the sun on Jungfrau Joch and Saint Moritz in Switzerland, and on the North Sea. Individual sensitivity shows extraordinary variation The action decreases with decrease of the dose. Patients become tolerant, possibly because of decreasing amount of lighter non-oxidized melanin. If the skin is made anemic by pressure, the

darkening does not occur presumably because of decrease in supply of available oxygen.

The indirect mechanism is produced by the sunburn spectrum, between 280 mμ and 320 mμ. Edwards and Duntley [30] exposed the skin of an adult male, which had not been exposed to ultraviolet irradiation for 2 years, to the midday sun in Boston. By means of the Hardy recording spectrophotometer hyperemia was seen to be pronounced in 2 hours, with the maximum in 11 hours. They determined that increase in melanin was apparent in 2 days, with maximum on the nineteenth day. At 1 month, melanosis started to diminish, and at 9½ months the color of the skin was the same as before exposure. Hamperl et al [31] stated that exposure to the sunburn spectrum is followed by photochemical breaking up of nucleic acid in the nucleus, which, in turn, causes the erythema, with an inflammatory reaction. Making the skin anemic did not prevent the reaction, as in direct melanosis. Following this erythema, pigment appears first in dendritic melanocytes in the basal layer of the epidermis. Pigmentation varies in degree with intensity of dosage of ultraviolet irradiation. However, in extremely severe sunburn with formation of bullae, the resulting hyperpigmentation may be decreased.

Sensitivity to ultraviolet irradiation varies in different individuals. Tolerance to repeated exposure results from two mechanisms. If the exposure is increased slowly the stratum corneum thickens (Miescher [28]) even in lightly pigmented persons, and acts as a mechanical protector. As the skin tans, the melanin contained therein (in supranuclear caps) also acts as a protective screen against short wave ultraviolet irradiation. Dark-complexioned persons are least sensitive but even in the African Negro erythema occurs, although it is identified with difficulty and melanosis appears on areas exposed to the sun.

The first sign of pending melanosis from indirect action is in the form of positive tyrosine and dopa reactions, with little or no melanin demonstrable by the silver reaction. The dopa reaction decreases in degree as the epidermis becomes pigmented.

In some patients who seem to tan poorly some chemical change takes place in the skin, shown by subsequent developer

Hamilton and Hubert [32] found that male hormone exerts such a developing action. Hypogonadal men were treated with ultraviolet irradiation, with no evidence of tanning. Subsequent administration of testosterone proprionate was followed by tanning. A similar situation was reported by Jodar [33]

A child aged 9½ months, showed extreme pallor. He was given 18 ultraviolet exposures in a physician's office at intervals of 1 week, without tanning. He was then given 180 ml of citrated blood from his mother. The next day the mother reported that the skin was yellow and he subsequently developed a light tan color with a lighter area around each eye, corresponding to that covered by the goggles during ultraviolet irradiation.

This report suggested a lack of precursors of melanin (tyrosine and phenylalanine) in the blood in sufficient quantities to allow for the usual tanning. It was assumed that the pigment producing enzymes were activated and remained in latent form until the transfusion.

Photosensitization. GENETIC. The most common, if not the sole, example of genetic photosensitization is xeroderma pigmentosum. It is characterized by an initially normal or pronounced reaction to ultraviolet irradiation, with prolongation of the erythematous reaction. The reaction recedes slowly and, if repeated, is followed by increased solar melanosis, later atrophy and telangiectasia. Pronounced hypersensitivity to grenz rays, roentgen rays, and alpha rays has also been reported. The offending rays have been in the sunburn spectrum (280 mm to 310 mm). Keratoses followed by prickle cell carcinoma are the rule. Members of the Caucasian races are most often the victims of the malady, but the disorder has been reported in the darker races: Chinese, Samoan, North African and full blooded Negro. Consanguinity of parents is prominent. Lynch [34] reported it in 17 to 59 per cent of cases, while Darier stated that 100 consanguineous marriages will produce 11.8 cases of xeroderma pigmentosum. Related parents are first, more rarely second cousins.

Among the tumors on exposed areas are angiomas, keratomas, keratoses, cornu cutaneum, prickle cell carcinoma, melanotic carcinoma, and melanoma. The last-named is spindle celled, and

The reports of Starck in 1944–1945 [42] and Billsario in 1952 [43] on photosensitization dermatitis due to handling of parsnips were preceded by 50 years by the report of J. C. White of Boston in 1897 [44] of an identical situation. A woman had washed with a cloth five bushels of recently dug parsnips. Inflammation began on the following day and the hands and wrists became greatly swollen. White made a diagnosis of dermatitis venenata and did not mention exposure to sunshine or postinflammatory sensitization melanosis. *Present knowledge makes it certain that the process was* photosensitization, which was not appreciated at the time.

One of the earliest, if not the first, reports of the influence of the sun, and probably the earliest tests, were those of Lewin in 1913 [45] who reported the cases of 53 men and 50 women who complained of itching while working in a cable factory in which crude coal tar pitch was incorporated into paper tubes. Thirty-two women and nineteen men itched only when exposed to the sun. Patch test to solution of coal tar N.F. and 5 per cent solutions of crude coal tar in acetone, alcohol, carbon tetrachloride, chloroform, and ether followed by irradiation with mercury vapor quartz and carbon arc lamps were negative. When the materials were applied for 3 days and the areas treated with ultraviolet irradiation, erythema appeared more rapidly on the painted areas. When a wetting agent was added to crude coal tar solution in carbon tetrachloride, the reaction was more intense than without the wetting agent. Freund [46] described four instances of intense pigmentation in irregular areas after the use of Eau de Cologne. Experimental rubbing in of both Eau de Cologne and oil of bergamot with subsequent sun bath was followed by melanosis. Several authors reported negative results to application of oil of bergamot, and even stated that it protected the skin from the ultraviolet irradiation. It was soon realized that, in order to photosensitize, *the material must be rubbed in.*

Guillaume in 1927 studied the photosensitizing effect of eosin, erythrosin, methyl violet, and acridine. He obtained sensitization to light bands of the complementary wavelengths (wavelengths absorbed by the dye) only after scarification of the horny layer had permitted entry of the dye into the prickle cells. If they did

not penetrate the stratum corneum, they only acted as a protective filter The Grotthus-Draper law states that only light which is absorbed can produce photochemical action. For this reason, the wavelength responsible for the action of different substances varies to some degree. The wavelengths attributed to various agents by different authors are as follows:

> Parsnip Active range 320 mμ to 366 mμ, and in lesser degree of 264 mμ to 280 mμ and 313 mμ, most pronounced at 366 mμ
> Furocoumarine from several plants 334 mμ to 366 mμ
> Oil of Persian lime 310 mμ to 370 mμ (Sams)
> Oil of bergamot 280 mμ to 410 mμ; max. at 311 mμ
> Crude coal tar 350 mμ to 450 mμ; most active at 320 mμ to 405 mμ, 390 mμ to 500 mμ (Foerster)

PHYTOPHOTODERMATITIS. Photosensitization caused by the products of plants, some of which have already been mentioned, have been included by Klaber [47] under the above designation. The plants are those which produce volatile oils, and are given in Table 6-a. The oils contain furocoumarines, which will photosensitize everyone if the material is properly applied. It must be rubbed into the skin, after which the area must be exposed for a time to ultraviolet irradiation, preferably from the sun. Light complexioned persons usually notice dermatitis in the area, followed by some pigmentation, but dark complexioned persons notice minimal inflammation followed by considerable melanosis. Sams [48a] reported the cases of 11 patients with sensitization dermatitis from oil from the rind of the Persian lime. By use of filters, he determined that the causative wavelength of ultraviolet irradiation was 310 mμ to 370 mμ. He ascertained that the concentration of the photodynamic agent, length of time of exposure, location of application, and previous irradiation determine the intensity of subsequent dermatitis. Later [48b] he mentioned that he had seen 290 patients with photodermatitis, in 186 of which it was due to application of lime oil. He added a group of slightly different eruptions, some of which were caused by sun screen preparations. There was no reaction to patch test, but application of ultraviolet irradiation to the area showed sensitivity to Neo-A Fil in one patient. The dermatitis does not confine

itself to the originally involved area but tends to spread over larger areas of the body. This new group is more difficult to study and evaluate than the ordinary phytophotodermatitis.

A group of patients with sensitization melanosis of the face and neck includes Riehl's melanosis, poikiloderma of Civatte, melanosis from tar and oil and cosmetics. A typical case was reported by Wieder [49].

A chemist, aged 37, had had hyperpigmentation of the face and neck for one month. He was found to be reactive to benzanthrone and naphthalene, both of which contained some impurities, when the application was followed by exposure to a suberythema dose of ultraviolet rays from an air-cooled mercury quartz light. Melanosis followed in both instances. Microscopic section, which I had the privilege of studying, showed pronounced hyperpigmentation with severe dermal melanosis of the postinflammatory type.

This feature differentiates sensitization melanosis from a simple type, such as Addison's disease.

Roentgen and Radium Rays. Alpha rays from thorium X are the most potent producers of melanosis, possibly because they are absorbed most superficially. Peck [50] and Becker, Jr., et al. [51] have shown that application of thorium X to the skin results in pronounced indirect melanosis. The use of beta rays, grenz rays, longer wave roentgen rays (Fig. 6-4), and gamma rays from radium cause decreasing reactions, possibly because a decreasing percentage of the rays are absorbed in the epidermis.

Melanosis Calorica. In regions exposed to heat, erythema caloricum appears in a vascular pattern resembling that of livedo reticularis. In persons who tan well, melanosis appears in the involved area as a brown network. The usual cause is heat from an electric pad or hot water bottle, but ovens containing burning coals, such as are used by a chestnut vendor, have also been incriminated. Microscopic examination reveals overactivity of epidermal melanocytes with little or no pigment in the dermis.

A burn of the palm may result in patchy melanosis. One of my patients had leukoderma of the wrist and melanosis of the palm, both from the same burn. Duemling presented a woman with melanosis of the palm following a burn from phenol.

Tattoo. Tattoos are of two types, accidental and artistic. Accidental tattoos are seen in certain industries, such as the mining of coal, mill-wheel dressers, workers in silver and as powder burns following an explosion. Metallic particles of various kinds



Fig. 4-4. Melanosis and leukoderma following treatment with roentgen rays. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

are seen following explosion of chemicals in a metal container. Road dirt is ground into the skin. Artistic tattoos are applied with carbon (China ink), cinnabar or carmine (red), cobalt blue, and viridian green or hydrated chrome oxide. Other colors are also used. After tattoo, the pigment is located in the papillae and dermis. Red pigment disappears in the tissue before the others; black rarely disappears entirely.

Removal of tattoo is not easy to attain. Powder stains or road dirt can sometimes be eliminated by repeated punch removals of particles along the tattooed line. Small tattoos may be excised. Larger tattoos may be treated by: first, the Variot method [52]

which consists of multiple needle tattooing with 50 per cent tannic acid followed by application of silver nitrate stick and in which a large eschar separates; secondly Darier's scarification plus application of phenol, or thirdly scarification plus potassium permanganate crystals. Lacassagne [53] prefers the last named method. Dubreuilh [54] shaved off the superficial skin and replaced it by a Thiersch graft. Plastic removal with replacement by a skin graft can now be carried out with good result. Dermabrasion has been only partially successful, because of the depth of the tattooed particles.

Melanosis in Internal Medicine

The various internal medical disorders that tend to generalized melanosis are given in Table 6-3, and those with a penchant for localized melanosis in Table 6-4. The prototype for generalized melanosis is Addison's disease. Hypoadrenocortical melanosis was first described by Addison in 1849. He stated that the skin was of

Table 6-3 MELANOSIS IN INTERNAL MEDICINE—GENERALIZED

Addison's disease
Hyperthyroidism
Rheumatoid arthritis (including Felty's syndrome, or Chauffard-Still disease)
Macrocytic anemia in children
Abdominal tuberculosis
Abdominal tumors
Hemochromatosis
Hodgkin's disease and other blood dyscrasias
Polycystic kidney and or adrenal
Biliary cirrhosis
Anorexia nervosa

a dark hue, as though the patient had descended from colored parents. The scrotum and the penis are darkest and the palms and soles the lightest. The darkest portions of the body become darker and sites of friction darken. The vermilion border of the lips and buccal mucosa show grayish plaques.

The prevailing theory of the mechanism of hyperpigmentation in Addison's disease is that failure of the adrenal glands to produce adrenal corticosteroids reduces their inhibition of pituitary

Table 6-4 MELANOSIS IN INTERNAL MEDICINE—LOCALIZED

Perioral lentigo profusa (Peutz Jeghers-Touraine [57-59])
Myxedema
Sprue
Café au lait spots in multiple neurofibromatosis
Melanotic plaques in Albright's syndrome
Simmonds' disease
Kala-azar
Schistosomiasis
Cushing's syndrome
Werner's syndrome
Acanthosis nigricans
Scurvy
Chloasma
Porphyria cutanea tarda

production of MSH. This results in excess production of MSH and subsequent melanosis. MSH has been studied by zoologists for many years and has been demonstrated in the urine of human beings during pregnancy usually by injections into hypophysectomized frogs. In patients with pituitary deficiency systemic melanosis may be lacking in Addison's disease.

Microscopic study of a cutaneous section shows hyperpigmentation, limited almost exclusively to the basal portion of the epidermis; hence, the clinical color is brown. Treatment of Addison's disease consists of administration of steroids

Generalized melanosis in abdominal tuberculosis, abdominal tumors, and Hodgkin's disease is attributed to involvement of abdominal nerves, celiac plexus, etc. If the adrenals are involved by the tumor the disorder falls in the realm of Addison's disease. Treatment depends on the presenting disease.

Melanosis in hemochromatosis has been explained in two ways First, infiltration of the adrenals by hemosiderin-containing cells produces Addison's disease. Secondly presence of hemosiderin in the skin causes competition for sulfhydryl groups by the iron which it contains, so that the inhibitory action of the sulfhydryl groups is lessened, hence production of more melanin. The metallic gray hue of the skin is caused by deposition of hemosiderin about the acini of the sweat glands, where it first appears later deposition of hemosiderin is seen in the other portions of the dermis.

Treatment of hemochromatosis consists of medical management, usually including treatment of severe diabetes (bronze diabetes)

Perioral Lentigo Profusa. In 1896 Hutchinson [55] presented both of dark brunette identical twins, who developed multiple melanotic macules about the mouth and lips, on the vermilion borders and oral mucosa at the age of nine years. Weber [56] in 1919 related that one twin had died at the age of twenty from intestinal intussusception. Autopsy was not performed, but it was assumed that intestinal polyposis was causative Peutz [57] reported the cases of a father his two sisters, and five of his children. All had lentigo profusa about the mouth. Three of the children had nasal polyps and probably also intestinal polyposis. There was one early carcinoma in a polyp. Jeghers et al. [58] reported ten cases of the syndrome. Some patients had lentigines on the hands and feet. At present this disorder is known as the Peutz Jeghers syndrome Microscopic section showed simple melanosis. *Touraine [59] presented a rather extensive array of* developmental anomalies associated with centrofacial lentigines, which are listed in Table 6-5.

The pathogenesis of the café au lait spots in von Recklinghausen's neurofibromatosis is not well understood. Masson has explained them as pigmentary macules at the terminations of nerves on which the neurofibromas form. Their chief value is in diagnosis of the *forme fruste* of the disease in which only the macules are evident. Crowe and Shull [60] found that any person with more than six café au lait spots which exceed 1 5 cm in broadest diameter must be presumed to have neurofibromatosis, even though the family history is negative. Since the pigmented plaques in Albright's syndrome are in the same region of the body that are involved in osteitis fibrosa cystica, some connection between the two processes may be assumed.

Acanthosis nigricans appears as one of two types, usually known as benign and malignant. According to Curth [61] who has made a special study of the disorder if it appears before or at puberty it is apt to be benign, in which type regression has been observed following the peak of adolescence If the disorder has its onset

Table 6-6 DISTURBANCES OF DEVELOPMENT WITH CENTROFACIAL LENTIGO PROFUSA

Anterior
- Olympian forehead
- Coalescence of eyebrows
- Absence or separation of upper incisors
- Disturbance of dental implantation
- Keel-shaped thorax

Posterior
- Hypertrichosis of vertebral groove
- Coccygeal dimple
- Cervicothoracic kyphosis
- Scoliosis
- Lordosis
- Disturbances of nervous system
  - Double talipes valgus
  - Nocturnal enuresis
  - *Palmar and plantar hyperhidrosis*

Lateral
- Asymmetry of areolae and breasts

Neuropsychic
- Infantile hemiplegia
- Convulsions
- Epilepsy
- Mental defects
- Behavior problems

Miscellaneous
- Flat hemangiomas
- Chagrin skin
- Keratosis pilaris
- Hypotrichosis
- Anodontia
- Familial psoriasis
- Adiposogenital dystrophy

Tumors
- Polyposis, familial or isolated
  - Intestinal
  - Nasal
  - Gastric
- Cyst of precocious ovary

SOURCE: A. Touraine [50].

after puberty it tends to be of the malignant type. In 20 per cent of cases, onset of the malignant type precedes development of malignancy. Onset of malignancy results in worsening of the disorder. After the treatment of carcinoma, acanthosis nigricans may subside or even disappear but it invariably reappears with

renewed signs of cancer activity The associated malignancies are all adenocarcinomas, 92 per cent from the stomach or abdominal cavity and 8 per cent in the breast, lung, etc. They are highly malignant and characterized by early metastases or inoperability The average duration is 12 months.

Difficulty in locating the neoplasm and removing it is illustrated by O'Leary's experience [62] Three patients with the adult type of acanthosis nigricans were given a thorough clinical survey including extensive roentgen ray studies of the gastrointestinal tract, which elicited no clinical or laboratory evidence of abdominal cancer All three patients were given a laparotomy with thorough exploration of all possible viscera. No evidence of cancer could be found. Within 5 months the first patient returned with a tremendous abdominal cancer involving primarily the liver from which he died shortly The second patient developed an apparently primary carcinoma of the stomach, from which he died in 6 or 8 months with visceral metastases. The third patient was alive after 5 or 6 years, still with his acanthosis nigricans.

The lesions of acanthosis nigricans appear in the axillae, groins, about the neck and elsewhere in the form of melanotic velvety verrucous plaques. Microscopic picture shows papillary overgrowth with folding of the epithelium into a rugous pattern. There is no true acanthosis. The basal layer of the epidermis is hyperpigmented with some pigment in the dermal melanocytes.

Treatment consists of search for malignancy and its removal or treatment if possible.

Chloasma. Better called melasma, chloasma is characterized by patchy melanosis on various parts of the face, the forehead, cheeks, and, sometimes, side of the neck. It is more frequent in women than in men and sometimes appears in association with pregnancy or pelvic disorders, when it is known as chloasma *uterinum.* The color is yellowish brown, which becomes darker on exposure to the sun. Guldberg [24] produced chloasma by injection of folliculin, an estrogenic hormone. The patients developed the melanosis of pregnancy plus chloasma.

Treatment of chloasma consists of strict avoidance of ultra

violet irradiation, and application of a bleaching cream, such as Benoquin ointment or zinc sulfur paste.

Porphyria Cutanea Tarda. The first symptom of this disease, which has been studied extensively by Brunsting [63] is usually formation of bullae at sites of friction. Melanosis and hypertrichosis may also be present, as reported by Turner and Obermayer [64] The causative rays have a wavelength of 300 mμ to 650 mμ. Many of the patients have liver disease, usually alcoholic cirrhosis, more rarely neoplasm. Treatment is directed toward the cirrhosis and search for neoplasm.

Central Nervous System

The various disorders of the central nervous system are listed in Table 6-6. A contribution on Schilder's disease by Derbes et al.

Table 6-6 MELANOSIS (Central Nervous System)

- Acromegaly
- Catatonic schizophrenia
- Paraplegia
- Diffuse cortical atrophy
- Nervous excitation
- Injury
- Ependymoma of third ventricle
- Schilder disease
- Hepatolenticular degeneration
- Fanconi disease
- Niemann-Pick disease

[65] discusses many of the neurogenic pigmentations. A recently described entity [66] ataxia telangiectasis, is characterized by cutaneous and mucosal telangiectases and macular melanosis. One autopsy showed cerebellar degeneration.

Postinflammatory (Table 6-7)

Almquist [67] stated that certain inflammatory processes in the skin by purely infiltrative cells, plasma cells, lymphocytes, and others, as a result of nonspecific destruction of these cells, are followed by melanosis. Rothman [68] presented the hypothesis that in inflammatory skin diseases, the sulfhydryl compounds in the melanocytes are oxidized or otherwise destroyed, thus per

mitting tyrosinase to act on tyrosine and produce melanin. Certain disorders are more apt to be followed by hyperpigmentation, namely lichen planus and lichenoid dermatitis, vagabondism, photosensitization dermatitis, pinta, and incontinentia pigmenti. The incontinentia of the last-named seems to represent merely postinflammatory loss of pigment from the epidermis, which is phagocytosed by the melanophages in the papillae and superficial dermis, where it remains, even after the inflammation has subsided, for about 8 months. The dermatologist should be familiar with the various ectodermal and mesodermal defects that have been reported in the various cases of incontinentia pigmenti, so that he can advise the parents of children with this disorder. Postinflammatory melanosis is characterized by a grayish hue caused by the presence of melanin in the papillae and dermis. It is more frequent in individuals with a good tanning potential than in persons who tan poorly.

Lipomelanic Reticulosis. This designation was applied by Pautrier and Woringer to a combination of postinflammatory

Table 4-7 POSTINFLAMMATORY MELANOSIS

- Varicella
- Measles
- Syphilitic papules
- Lichen planus
- Keratosis follicularis (Darier)
- Herpes zoster
- Urticaria with pigmentation
- Fixed drug eruption
- Sensitization dermatitis
- Palmar melanosis
- Pinta
- Vagabondism
- *Trichophyton sulfureum* dermatitis (extensive)
- Scleroderma
- Pityriasis rubra
- Exfoliative dermatitis
- Lipomelanic reticulosis
- Incontinentia pigmenti
- Dyskeratosis congenita with pigmentation, dystrophia unguis and leukokeratosis (Engman-Cole)
- Poikiloderma congenitale (?)
- Urticaria pigmentosa (?)



Fig. 6-3 Poikiloderma congenitale (Thomson). *Melanosis may be considered as prenatal or postinflammatory. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)*

melanosis and melanosis and lipoidosis of the regional lymph nodes. The disorder has also been called dermatopathic lymphadenopathy (Allen) It was at first thought to be a serious, often fatal malignant reticulosis, but it was soon realized that the

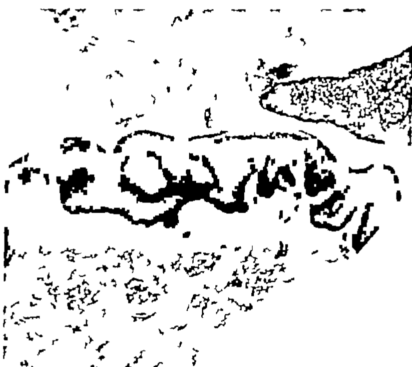


Fig. 6-6. Poikiloderma congenitale (Thomson). Melanin is confined to the epidermis, which suggests prenatal origin. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

cutaneous melanosis represented postinflammatory melanosis independent of whether the cause was benign or malignant, and that the lipoidosis and melanosis of the lymph nodes are an exaggerated form of such changes which occur normally

Riehl [69] found melanin in the lymph nodes of two of four patients with Addison's disease. Schmorl [70] found melanin in lymph nodes of two mulattoes and two Negroes, and in five

patients with Addison's disease. With regard to lipids, Stheeman found them in lymph nodes of all children, even as young as seven months. He injected dyed olive oil into the extremities of children dying with miliary tuberculosis and identified it in the regional lymph nodes at autopsy

If the dermatitis, usually of the exfoliative variety stems from a malignant process, such as leukemia or reticulum cell sarcoma, the outcome is fatal, but if the cutaneous inflammation is in the form of erythroderma secondary to lichen planus, as reported by Obermayer and Fox [71] in a seventy-year-old man, or to psoriasis, it subsides in due course.

Urticaria Pigmentosa. Better known as mastocytosis (pigmented or nonpigmented) urticaria pigmentosa has been recently discussed by Nickel [72] The reader is referred to his presentation for accurate and complete details of modern ideas on the subject.

Medicamentous

Certain drugs have produced melanosis of the localized or generalized types. Localized forms are usually postinflammatory melanosis, such as that of a fixed drug eruption or lichenoid drug eruption. The most common generalized medicamentous melanosis is that produced by arsenic, which was formerly frequently administered in the form of Fowler's solution. While the drug is administered less often than previously arsenical melanosis is sometimes seen as a result of use of arsenical sprays in orchards. It is characterized by light brown melanosis, with nonpigmented areas about the follicles. It is usually associated with arsenical keratoses of the palms and soles. The chief implication of this melanosis is the possibility of arsenical cancer which may appear many years after the use of the drug or spray Prophylactic administration of BAL may improve the prognosis, but little can be done after pigmentation has appeared.

Mucosal (Table 6-8)

The mucocutaneous junctions and adjacent mucosae contain melanocytes, which occasionally become hyperactive and pro-

duce clinical melanosis in the form of brown to black macules. The disorder is more frequent in dark-complexioned persons and is present so frequently in members of the darker races that it can be considered more or less normal. Drummet [73] compared the complexion of 600 Negroes with various shades of pigment in the lower one-half of the face with the color of the oral tissues. Most gingival pigmentation was proportionate to the cutaneous pigmentation, but the fact that some dark Negroes had no oral melanosis suggested that the association between the two areas is not constant.

Conjunctival melanosis is seen in lighter-complexioned persons in avitaminosis A, lentigo, and premalignant melanosis (Reese) Oral melanosis is seen in Addison's disease, Peutz Jeghers syndrome, porphyria, after administration of corticotropic hormone probably containing MSH, Atabrine glossitis, and in tobacco

Table 6-8 MUCOSAL MELANOSIS (More Prominent in Dark Races)

- Conjunctival
  - Lentigo profusa
  - Addison's disease
  - Racial melanosis, including cornea
  - Avitaminosis A
  - Xeroderma pigmentosum
  - Lentigo
  - Lentigo maligna
  - Arsenical melanosis
- Oral
  - Lentigo profusa
  - Addison disease
  - Tobacco chewers
  - Atabrine glossitis
  - Postradiation therapy
  - Melanoplakia
- Vaginal-cervical
  - Following prolapse
  - Racial melanosis
  - Melanoplakia

chewers. Lingual melanosis was reported by Rattner and Ginsberg [74] in a Negro woman who received repeated radium therapy for a parotid tumor

Vaginal and cervical melanosis were reported by Acton to be

frequent in women in India and were found by Babes [75] in a woman with uterine prolapse.

Ochronosis (Table 6-9)

This name was given by Virchow to a disorder characterized by grayish brown or black discoloration of cartilage, with pigmentation of the skin, adjacent mucosae, and fingernails. Laymon [76] gave an excellent discussion of the disease in 1953, in connection with a patient who had an unusually hyperpigmented skin. The disorder is divided into two types exogenous and endogenous. The exogenous type, called carbolochronosis, results from absorption of phenol following long-continued application of the chemical to open cutaneous lesions, usually stasis ulcers. One of the latest publications was that of Berry in 1932 [77] of the fourteenth reported case, of a bedridden woman, aged fifty-seven, who had applied phenol dressings to her legs for 30 years, presented typical ochronotic pigmentation Goldberg [78] maintained that pigmentation is produced by a hydrooxylated phenol derivative. In contrast to the fifteen or so reports of carbol ochronosis, there are slightly less than a hundred reports of endogenous ochronosis, which differs chiefly by the presence of arthritis, absent in the exogenous form.

Table 6-9 OCHRONOSIS

- Exogenous
  - Long-continued absorption of phenol
  - Polymerization of oxyphenyl derivatives in tissue to form brown pigment
- Endogenous
  - Alkaptonuria
  - Polymerization of homogentisic acid (2,5-dihydroxyphenylacetic acid) in tissue to form brown pigment

Ochronotic pigment does not give silver reaction for melanin. Collects in cartilage bone and connective tissue causing bluish discoloration.

In the endogenous variety associated with alkaptonuria, cutaneous and mucosal discoloration are produced by presence of a homogeneous light brown pigment, a polymer of homogentisic acid (2,5-dihydroxyphenylacetic acid) a degradation product of

tyrosine. Normally homogentisic acid would be converted to carbon dioxide and water but in alkaptonuria, this reaction is blocked, and homogentisic acid is retained in the tissues, to produce the brown pigment, which does not give the silver reaction for melanin. There are less than two hundred reports of alkaptonuria in the literature- hence, about half of them have proceeded to ochronosis, although it has been stated that they would all do so if the persons lived long enough.

Metallic (Table 6-10)

Of the various metallic compounds deposited in the skin, silver [79] has been the worst offender Seen less frequently than formerly patients with argyria present a grayish tint to their skins. Microscopic section shows fine grayish granules in the dermis, best seen on dark field illumination Treatment is unsatisfactory If the patient has a good tanning potential, tanning of the skin produces a more pleasant tint Chrysiasis differs from argyria by its greater prominence on exposed areas and slightly purplish hue. It has been seen less frequently since large doses of gold compounds for tuberculosis have been discontinued.

Table 6-10 METALLIC PIGMENTATION

- Argyria
- Hydrargyria
- Chrysiasis
- Bismuthia
- Iron tattoo
  - Traumatic, including addicts
  - Wet dressings
  - Hemosiderosis
    - Schamberg' disease
    - Lichenoid pigmentary dermatoses (Gougerot Blum)
    - Purpura annularis telangiectodes (Majocchi)
    - Gaucher's disease
    - Hemochromatosis
    - Stasic dermatitis

Wet dressings of ferrous salts, when used in alternation with aluminum subacetate, tend to produce a brownish staining of denuded tissue. The brownish color due to the presence of iron acetate, persists for many months and finally disappears.

Bismuthia was first described by Gougerot and Blum in 1935 [80] A patient had received much bismuth for treatment for syphilis, along with some arsenic. Diagnosis was made of pseudo-argyria caused by bismuth. There was a diffuse slaty color of the face and trunk and numerous slaty plaques on the buccal mucosa. The diagnosis of bismuthia was first made by Leuth, et al. [81] A patient had taken bismuth for a long time for treat ment of diarrhea. The skin was of deep gray blue color with a metallic sheen. The hair had a deep mahogany shade. Pigmenta tion was most pronounced on the forehead, face, neck, and dorsa of the hands.

Hemosiderin is found in the skin on the legs in most individuals beyond middle life, and tends to persist. The color varies from brown through gray to black. Dermatoses characterized by hemo-siderin deposits, Schamberg's progressive pigmentary dermatosis, lichenoid pigmentary dermatosis of Gougerot and Blum, and Majocchi's purpura annularis telangiectodes tend to clear entirely but are apt to recur or progress at the borders. Hemochromatosis shows a metallic gray hue caused by deposition of hemosiderin about the sweat gland acini. A brownish hue as in Addisonism is also sometimes seen.

LEUKODERMA

The designation *leukoderma* was introduced by Neisser in 1883 for hypopigmentation in syphilis. The term is not quite accurate, since amelanotic skin is not white but shows a pinkish shade from the vascular bed. It has been used since that time to designate amelanotic skin and also skin that has been partially depig mented. Almquist [67] stated that certain pathologic processes probably by toxins of specific cause or by secondary infection with pus germs, have destructive influence on melanogenesis with resulting leukoderma.

Leukoderma has many causes, listed in Tables 6-11–6-15.

Prenatal

Partial Albinism. Localized prenatal leukoderma has been called partial albinism, local albinism, circumscribed albinism,

achromic nevus, white nevus, and nevus depigmentosus. It has also been called skin spotting or piebald skin. The disorder consists of various combinations of a white forelock and/or one or more depigmented plaques on various parts of the body It is dominant, tends to be familial, and to occur in the same cutaneous area in affected members of a family Pearson [82] stated that when a pure race is crossed with a hybrid from races with markedly different degrees of pigmentation, then piebalds are likely to appear *de novo* The depigmented spots remain the same throughout life, although Pearson reported some restoration of pigment in one child. Feeblemindedness is an occasional accompaniment. Partial albinism tends to run true to form. Sanders [83] found partial and total albinism in different members of the same family in only 2 out of 140 families.

Total Albinism. The more common total albinism, usually semi total, since Waardenburg [84] stated that traces of pigment can almost always be seen in so-called total albinos, is a recessive trait. Consanguinity is frequent. Garrod [85] reported that while 8 per cent of marriages in England are between first cousins, in albino families they constitute 40 per cent. The skin of a total albino is pink, as are the irises. In the Negro, the skin is pink, and the irises rarely may be pink but are usually blue to hazel to cinnamon brown. The color of the hair in the Caucasian [86] is bluish white, rose-white, or yellowish white- in the Negro [8] it is pale straw to yellowish to reddish. The longest record of human albinism dates from 1681 when Wafer first reported albinos among the San Blas Indians of Eastern Panama, in whom albinism is present in 0.7 per cent of the members.

Albinism is caused by absence or inactivity of tyrosinase in melanocytes in the skin, which are present in normal numbers and can be stained by nerve stains, such as methylene blue or gold salts, but gi e a negative dopa reaction [51] The practical disadvantage of total albinism results from ocular difficulties (photophobia and nystagmus) and lack of the protection that melanin affords to the skin from actinic irradiation. As a result, solar keratoses with subsequent carcinoma, dermatitis, and im petiginization are common. Carerj [88] reported nonpigmented

melanoma in albinotic white skin, but [illegible] in a Negro albino.

Treatment of albinism consists of pr[illegible] sunlight and treatment of any prese[illegible]

Acquired

Physical causes of leukoderma are lis[illegible] severe inflammation is necessary to pr[illegible]

Table 6-11 LEUKODERMA

- Prenatal
  - Albinism
    - Partial
    - Total
- Acquired
  - Physical
    - Cold permones
    - Heat
      - Burns
        - Mild, temporary
        - Severe, permanent (destruction of [illegible]
  - Mechanical
    - Scratching neurodermite (Clevelan[illegible]
  - Actinic
    - Ultraviolet
    - Roentgen rays
    - Thorium X alpha rays
    - Radium beta and gamma ray
    - Isotopes beta and gamma rays
  - Chemical
    - Monobenzyl ether of hydroquinone [illegible] and artificial rubber—leukoderma [illegible] shield, guard for garter clasp [illegible] doll, apron, ironing-board cover
    - Benoquin ointment (20%) and [illegible]

production of melanosis. A scar from [illegible] mented.

Chemical action of monobenzyl ether [illegible] oxidant used as Age-rite Alba in art[illegible] rubber and in Benoquin ointment (El[illegible] menting properties, results in temporary [illegible] various natural and synthetic rubber [illegible] caused depigmentation are given in Tab[illegible]

allergic contact dermatitis has been associated. Treatment consists of appropriate measures for any associated dermatitis, and avoidance of contact with such rubber articles.

The causes of postinflammatory leukoderma are given in Table 6-12. In many instances the change is partial and probably re-

Table 6-12 POSTINFLAMMATORY LEUKODERMA (Severe inflammation)

- Dermatitis venenata
- Psoriasis
- Parapsoriasis
- Pityriasis rosea
- Herpes zoster
- Keratosis follicularis (Darier)
- Eczema
- Urticaria
- Lichen planus
- Epidermolysis bullosa (dystrophic)
- Scleroderma
- Neoplasms
- Medicamentous dermatitis
- Xeroderma pigmentosum
- Infections
  - Syphilis
  - Leprosy
  - Yaws
  - Pinta
- Leukomelanoderma
  - Generalized exfoliative dermatitis
  - Localized dermatitis

versible, while in others, sufficient damage to melanocytes has resulted to make the depigmentation permanent. The leukoderma which follows the blue stage of pinta is said to be permanent and I was unable to identify melanocytes in microscopic sections from the depigmented plaques, as can be done in vitiliginous patches [89]. It would be interesting to study the depigmented patches in pinta by the split-skin method.

Treatment of postinflammatory leukoderma consists of staining the area if it is small enough to make it feasible. Sezary [90] produced repigmentation of an achromic plaque in leprosy by Uhlmann's method (rubbing in of 10 per cent oil of bergamot followed by irradiation from a mercury vapor lamp).

Leukomelanoderma

A combination of melanosis and leukoderma is occasionally seen following severe dermatitis, usually generalized exfoliative dermatitis as reported by Cannon and Karelitz [91] At times, the disorder is seen following dermatitis of more limited extent. The following report is illustrative

A man, aged 59, had had severe dermatitis of the hands, forearms, arms, and neck for three years. On recession of the dermatitis, leukodermatous patches were seen (Fig. 6–7)

Leukomelanoderma has been reported in Negroes in a complete or subtotal distribution. Tauber [92] published the case of a Negro, aged thirty two, who had had generalized dermatitis at the age of fifteen, followed by total loss of body pigment. After being depigmented for 13 years, with daily exposure of the body to ultraviolet irradiation and to sunshine a few isolated spots of pigment appeared on the face, neck, and shoulders. Such return of pigment always arouses suspicion that the disorder may have been vitiligo rather than leukomelanoderma.

Treatment of leukomelanoderma consists of removing any discovered cause and staining the skin if feasible.

Hypopigmentation

Decrease in pigmentation without actual leukoderma is seen in a variety of disorders (Table 6-13) One of the most common

Table 6-13 HYPOPIGMENTATION

Erythema streptogenes (pityriasis alba, furfuraceous impetigo, streptococcal seche dartre olante vitiligo streptococcique pityriasis faciei)
Kwashiorkor
Pseudoachromia parasitica
- *Malassezia furfur*
- *Trichophyton*, including favus
- *Microsporon*
- *Epidermophyton*
- *Aspergillus*
- *Hemispora*
- Causation
  1 Pure filtering of ultraviolet irradiation
  2 Toxic effect of fungus on melanocytes
  3 Combination and or alternation of the tw

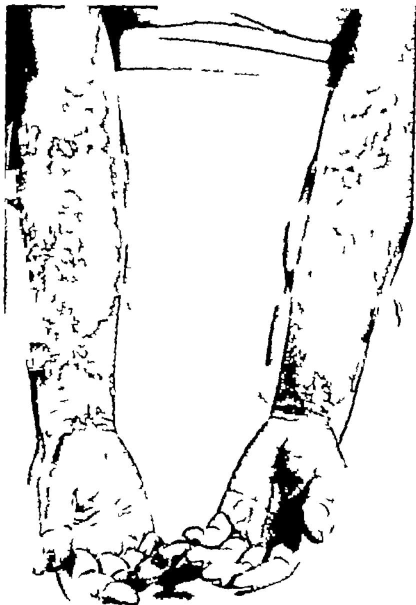


Fig. 4-7 Leukomelanoderma following severe dermatitis in man aged fifty-nine (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

forms has been called by several names which imply an infectious causation It has been seen most frequently in darkly pigmented persons, usually in the form of facial lesions, a few millimeters to a few centimeters in diameter consisting of scaly hypopigmented plaques. It was studied by Dobes and Jones [93] who cultured hemolytic streptococcus from six of eleven Negro children, *Staphylococcus aureus* from two, and *Staphylococcus albus* from two. Microscopic examination showed inflammation and partial depigmentation Treatment was carried out successfully with crude coal tar or oil of cade or ammoniated mercury ointments.

Tas [94] reported a larger series of 50 children with pityriasis simplex faciei. Mycologic cultures were all negative. Eleven bacterial cultures were negative. Positive cultures included hemolytic streptococcus, 1 nonhemolytic streptococcus, 2, *Streptococcus viridans*, 2, *Micrococcus pyogenes* var *aureus* 9; *M pyogenes* var *albus*, 18 *Bacillus subtilis*, 6; *Bacillus alcaligenes*, 2. Ten patients were treated systemically with penicillin, with no benefit. All patients received water soluble vitamin A, with no result. Local therapy was not mentioned.

Nutritional. A nutritional disease seen in Africa, known as kwashiorkor which means red boy is characterized by severe edema, labial and angular stomatitis, glossitis, diarrhea or steatorrhea, peculiar depigmentation of the skin over the entire body and a graying of the hair of the scalp with varying degrees of alopecia. It is said to follow weaning, at which time children are placed on a banana diet. It has been called infantile pellagra [95] Treatment consists of a high protein diet with vitamins. Gillman and Gillman [95] added powdered stomach to the diet.

Pena Chavarria et al. [96] discussed vitamin deficiency disease in Costa Rica, producing a form of pellagra which resulted in depigmentation and fragility of the hair Goldman [97] reported the cases of 14 children living in the southern Ohio area. Four had received sulfonamide medication, six had oxyuris infestation, and one had anchylostomiasis.

Pseudoachromia Parasitica. An apparent hypo- or depigmentation is seen in patients with extensive fungous infections, characterized by scaling, who have been exposed to tanning doses of

ultraviolet irradiation. The tanning occurs between the fungal lesions, which then, by contrast, appear hypo- or depigmented. There are three groups of authors who have attempted to interpret the process. The first believes that the hypopigmentation results



Fig. 6-8. Pseudoachromia parasitica in Negro aged twenty-four. (Courtesy of Veterans Administration Hospital, Long Beach, Calif.)

from a purely filtering effect of the fungus-containing scales. The second group believes that toxins derived from the fungus interfere with pigmentation. A third group believes that the cause may vary in different patients, depending on the strain of the fungus, and other factors.

The various organisms that have been incriminated are *Malassezia* which is responsible for most cases, *Trichophyton*, *Nocardia*, *Epidermophyton*, *Aspergillus*, and *Hemispora*. The following case report is illustrative

W. G., a Negro, aged 24, presented hypopigmented scaly plaques on the lateral surfaces of the neck (Fig. 6-8) present for 6 months extending downward onto the trunk. KOH preparation revealed *Malassezia furfur* and diagnosis was made of pseudoachromia parasitica.

In Negroes, there is the double factor of tanning between the lesions and hypopigmentation of the lesion itself because of the scaling.

Treatment consists of application of antiparasitic ointment, such as 5 per cent Asterol or 2 per cent salicylic acid and 3 per cent precipitated sulfur. In pityriasis versicolor treatment must be continued for some weeks in order to prevent relapse caused by spores in the hair follicles.

Hormonal

Pituitary deficiency results in hypo- or depigmentation, usually incomplete since some tanning may be elicited by ultraviolet irradiation. Cretins also have decreased cutaneous pigmentation. Plummer and Jaeger [98] reported the case of a dark-complexioned man who died with infiltrative glioblastoma of the pituitary. His skin grew lighter and the hair of the beard, lashes, brows, axillary and pubic regions became first lighter then sparse. The hair was light brown, thin, dry and brittle.

Central Nervous System

In addition to complete atrophy of the pituitary gland, leukoderma is seen in amyotrophic lateral sclerosis, tabes dorsalis, and the Vogt-Koyanagi syndrome.

Vitiligo

Vitiligo is the most common variety of acquired leukoderma, and appears in the form of sharply circumscribed, round, oval, or irregular depigmented plaques with hyperpigmented borders. The lesions are usually symmetrical, ordinarily confined to the cutaneous surface, but occasionally seen on the mucocutaneous junctions and adjacent mucous membranes. The onset is usually insidious, especially in light-complexioned persons, and attention

Table 6-14 LEUKODERMA

Hormonal
- Pituitary insufficiency
- Thyroid insufficiency

Central nervous system
- Complete atrophy of pituitary gland
- Amyotrophic lateral sclerosis
- Tabes dorsalis
- Vogt Koyanagi syndrome

Table 6-15 VITILIGO (Causation)

I. Trophoneurotic
- A. Sympathetic
- B. Psychic shock
- C. Noradrenalin at nerve endings (Lerner)

II. Hormonal
- A. Puberty
- B. Menstruation
- C. Pregnancy
- D. Menopause

III. Infections
- A. Syphilis (French authors)
- B. Typhoid fever
- C. *Spirillum* (Cederberg—19[illegible])

IV. Toxic and medicamentous
- A. Intestinal infection (Sahu—1955)
  1. Amebiasis
  2. Ascariasis
  3. Hookworm
  4. Giardiasis
  5. Bacillary dysentery
- B. Diodoquin, given for amebiasis (Fox—1910)

V. Inflammation
- A. Inflammatory border (Becker and Obermayer, Garb and Wise, Buckley and Lobitz)

VI. Associated dermatoses
- A. Neurodermatitis and lichen planus (Welander)
- B. Eczema (Kreibich)
- C. Lichen planus (Madden, Walzer, Becker)
- D. Alopecia areata (Anderson, Brown)
- E. Addison's disease (Addison, Barber)
- F. Neurotic excoriation (Becker and Obermayer)

VII. Pathogenesis
- A. Failure of ferment (Bloch, Becker)

is often called to the plaque by unexpected sunburn after ex posure to sunlight.

The various theories as to the causation of vitiligo are given in Table 6-15. The consensus today is that it is a functional dis ease.

Methods of therapy for vitiligo are given in Table 6-16 I have had success with the method given under functional therapy

Table 6-16 TREATMENT OF VITILIGO

1. Ultraviolet irradiation, with or without sensitizer
   - Oil of bergamot (10%)
   - *b* Bouchi oil from *Psoralea corylifolia*, by injection
   - 8-Methoxypsoralen, externally and internally
   - *d* Solid carbon dioxide
   - *e* Local injection of various substances
2. Metallic therapy
   - *a.* Arsenic-sodium cacodylate or arsylen
   - *b* Gold-sodium-thiosulphate (*Lindsay*)
   - Bismuth (with ultraviolet irradiation—Lortie)
   - *d.* Tattoo with Ag_2O, Ag_2S HgO, HgS Bi_2S_3, Fe_2O_3
3. Chemical irritants
   - *a.* Mercury
   - *b.* Chloral hydrate
   - Capsicum
   - *d.* Iodine
   - Chrysophanic acid
   - *f* Anthralin
4. Stains
   - *a.* Walnut, made from fresh green hulls
   - *b.* Artificial stains, brown in color
5. *Functional therapy*
   - *a.* Rest—repigmentation in Negro after 16 weeks in hospital with fracture (Trim and Sequira)
   - *b* Daily nap and sufficient nocturnal rest, sedation
   - Daily ultraviolet therapy; UVL erythema once weekly
   - *d* Restriction of activities

The most modern treatment has been the local application and/or the ingestion of 8-methoxypsoralen, a furocoumarine obtained from *Ammi majus* and supplied as Oxsoralen. Local application of the substance has been temporarily discontinued because of severe reactions to ultraviolet irradiation after its application. Adequate regulation of the amount of ultraviolet irradiation is difficult to attain.

Ingestion of Oxsoralen is made in doses of 20 mg taken at 9 A.M. with food. Exposure to ultraviolet irradiation should be taken 2 to 3 hours later preferably as sunlight. Length of exposure must be carefully regulated, the time depending on the



Fig. 6-9 Vitiligo with recurrent islands of melanin pigmentation after rest, sedation, and generalized ultraviolet irradiation following application of 10 per cent oil of bergamot (Courtesy of Veterans Administration Hospital Long Beach, Calif)

patient's tanning potential, geographic location, and the season of the year A suberythema dose is preferred, and increase should be gradual.

Ultraviolet irridiation has played a prominent role in the therapy of vitiligo. The earliest report was that of D W Montgomery in 1904 [99]

A Mexican boy aged 19, had had vitiligo since the age of five or six. He was exposed to a Finsen lamp (carbon arc burner with quartz lens system) for 10 minutes with a total of nine exposures starting on

April 25, 1903. On September 1, lesions on the face had become repigmented, and the hands nearly so.

On the other hand, Buschke [100] had tried both the Finsen and therapeutic carbon arc lamps without result but obtained repigmentation following a blistering reaction from a mercury vapor quartz lamp. Stein [101] verified this result and also obtained pigmentation following heat, solid carbon dioxide, and trauma. The pigment which the patient obtained eventually disappeared.

One of the earliest reports of fortification of the ultraviolet irradiation by a sensitizer was by Uhlmann [102] who applied bergamot oil to vitiliginous patches and exposed them to the sun. Pigment reappeared and remained for 9 months observation. Nadel [103] injected acridine and gave Trypaflavin orally along with artificial ultraviolet irradiation or natural sunshine. The new-formed pigment was identified as melanin.

Table 6-17 PROGNOSIS IN VITILIGO

Depends on duration of plaques the longer the duration, the poorer the prognosis.
Many authors do not give duration of plaques.
Patients do not cooperate very well.
8-Methoxypsoralen has the advantage that it can be taken from bottle.

Prognosis. Since I believe that vitiligo is a functional disorder great emphasis is placed on the necessity of rest. Failures of therapy can be avoided only in this way If the patch of vitiligo is of only a few months duration, it is possible to induce the pigment to return in all instances, but a regimen of rest and relaxation must be persisted in to avoid recurrence, since patients with vitiligo are restless and not too cooperative. Patches of long duration can be repigmented only with great difficulty

Nevus Anemicus

Although this disorder described by Voerner [104] does not represent disturbance of melanin pigmentation but rather lack of vascular supply in the area, it can be mistaken for depigmentation if not carefully observed The lesion shows lessened vascular

reaction on friction, as compared with the border. There is no satisfactory treatment.

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Norman Q Brill **7**

EMOTIONAL FACTORS IN DERMATOLOGIC DISORDERS

As RECENTLY AS 25 years ago the role of emotional factors in dermatologic disorders was rarely if ever mentioned in undergraduate medical school courses in dermatology The history of the gradual recognition of the importance of psychic factors in skin diseases, including some of the work in the early 1900s on producing skin lesions by hypnosis, has been reviewed many times by many workers, and I shall not attempt such a review here, those who are interested may read an excellent summary in Flanders Dunbar's book "Emotions and Bodily Changes (4th edition, 1954, *Columbia University Press, New York*) or in the monograph "Emotional Factors in Skin Disease, by E. Wittkower and B. Russell (1953, Hoeber New York)

By 1930, authorities like Stokes and Pillsbury [1] had concluded:

> The larger our experience and the more careful our search (of the literature) the more we are inclined to believe that in the urticarias and urticarial dermatitides of middle life, in the diathetic eczemas and rosacea, and even in the dermatoses which, like epidermophytosis, seem far removed from psychological considerations, the tension make-up, the personality defect, the conflict and anxiety the repression and

the complex have their place as causal influences, to be sought out and rectified side by side with, and sometimes even before, the correction of the more apparent physical dysfunctions.

Collaborative studies by dermatologists and psychiatrists grew more common, and in recent years there has been a veritable flood of reports on the role of emotional factors in skin disorders. As an introduction to the presentation on treatment, I shall attempt to summarize present day concepts, colored, of course by my own biases.

SKIN AS AN ORGAN OF EMOTIONAL EXPRESSION

That emotions may express themselves as bodily symptoms has been known intuitively for a long time. There are many phases in our language which are indicative of this understanding. Just as some phrases refer to the occurrence of gastrointestinal symptoms ("I can t stomach that, so-and so gripes me, "I can't swallow that) there are others which suggest the skin as an organ of expression of emotions. Apart from the obvious significance of blushing, or getting red in the face, we may "burn with indignation, or be "irritated, or sensitive, or something may get under our skin, or we may itch to do something, or "be in a sweat. Occasionally a person will say to another Don t break out in a rash instead of "Don t get so angry We can "itch for a fight, become pale with fright or anger glow or be dull and the term sweat it out has obvious connotations.

It is obvious, when one thinks about it, that people differ greatly in their interest in their skin. Some persons pay great attention to their skin s appearance others couldn t care less. In our culture a certain amount of such interest is normal and desirable and associated with a desire to appear attractive to others as well as to oneself. In general women seem to have a greater interest than men. From the effort parents must make to get children to wash their hands and faces and to bathe it would appear that children s interest in their skin is not as great as is grownups

It is a matter of common observation that there is a sudden

great increase in boys and girls interest in their appearance at puberty It is the time that a girl who has been content to lounge around in jeans is apt to do on her own what her mother may have spent years trying to accomplish—i.e., dress like a lady Similarly boys who rebelled at the idea of wearing a suit or a tie or a white shirt suddenly begin to dress up Their skin is one part of their appearance, and the coincidental increase in interest in their skin and in members of the opposite sex suggests a relation between interest in skin and desire to be sexually attractive.

One must first love oneself to feel capable of being loved. Self love (which is called narcissism) develops initially in children from the love and feeling of importance and worthwhileness they get from their parents, brothers and sisters, relatives, friends, teachers, and others.

Interest in an object or a person implies an emotional invest ment, and an interest that involves doing something good is an element in the emotion of love. Interest in skin then involves an emotional investment that has sexual overtones—which in psy chiatry we call libido.

Persons who invest an excessive amount of interest in their own skins (we use the words *own skin* to mean oneself")—who go to great lengths to obtain massages, special baths, even sunburns, etc.—are properly looked upon as narcissistic.

Why some people are more narcissistic than others and why some who are excessively narcissistic express it by exaggerated interest in their skin has no simple answer Undoubtedly there are constitutional factors which as yet we cannot define. Why some react more intensely to psychic trauma than others and why some react with one particular organ and not another we do not know However it is often possible to relate excessive narcissism to emotional hurts or feelings of being unloved in children (as if they were saying "If you don t love me, I'll love myself or as if one were saying "To love someone else exposes me to the possibility of being hurt, so I won t love anyone except myself since I won t hurt myself) Or it may be the result of a psychic regression to an earlier level of development (which is character ized by exaggerated narcissism) because of some real or fantasied

inability to deal with some conflict or situation in any other way An example of this is the child who begins to act like a baby again after the birth of a younger sibling. It is not just imitation—it is purposeful behavior even if unpopular and unwelcome with parents.

The question of why the skin becomes the organ of emotional expression in some patients remains to be answered. Why some patients develop anxiety states, others conversion reactions, others dysfunction of the stomach, colon, bronchi, or heart, and some others skin disorders as a result of emotional conflict is something we can only speculate about. Theoretically it occurs in certain individuals in whom the skin has been particularly libidinized. This may occur as a result of excessive or deficient stimulation of the skin of the infant by the mother (or mother substitute) it may be the accidental result of unusual attention to skin lesions in infancy that were of a nonpsychogenic nature; it might be the result of a purely accidental finding by the infant of a pleasurable response from self-stimulation of the skin that later was used for giving self-comfort in times of stress, unhappiness, loneliness, or anxiety—as some children do with genital stimulation. The skin can be employed as a symbol for a loving mother from unconscious memories of contact with the mother Even for adults it does not take any great stretch of imagination to associate certain skin sensations with memories of persons with whom they have had bodily contact

However all this is still just theoretical, and in the final analysis we are no more able to explain why the skin is chosen as the organ which expresses psychopathology than we are able to explain why diphtheria so often involves the throat rather than the stomach or lungs.

PSYCHIATRIC DISORDERS IN DERMATOLOGIC PATIENTS

The psychiatrist rarely has the opportunity to evaluate all patients with skin disorders. He is apt to see only those who do not respond to usual treatment or those who have obvious concomitant emotional disorders. He is therefore generally in a poor position to estimate the incidence of emotional disorders in

patients with skin diseases or to assess in a statistically convincing way the relationship between emotional and skin disorders.

It might be of interest to learn what the psychiatric disorders were in a very small sample of patients randomly selected from those who were referred to the psychiatric clinic from the dermatology department at the UCLA Medical Center In the last case described below the patient was seen privately and a more detailed outline of the development of his disorder is given in order to exemplify the kinds of psychic forces that may be operative in these types of patients.

A 30-year-old male with generalized alopecia was found to be suffering from an early paranoid schizophrenic reaction. He was having *marked marital difficulty and struggling with conscious homosexual* impulses and compulsive masturbation. He had itching of the scrotum and arms, when nervous, and maintained that his loss of hair on two occasions was brought on by emotional tension.

A 35-year-old married woman with generalized alopecia had suffered from a severe depression after the birth of her second child, 5½ years previous to being seen in the psychiatric clinic, and was referred to the psychiatric clinic because of a phobia. She was afraid that she would kill her three children while her husband was away Her generalized alopecia first occurred 3 years before at a time when she was under extreme nervous tension and unable to eat. The depression that she had had 5½ years before recurred after the birth of another child 1 year previously and again following the death of her mother

A 31 year-old single male was suffering from atopic dermatitis which he himself suspected was of emotional origin. He was found to be severely hypochondriacal, dependent, recurrently depressed, and struggling with homosexual impulses. He was actively homosexual up until the age of 19. The patient s mother suffers from asthma, his father and a younger brother suffer from spastic colitis. An older brother has eczema. The patient dreams that he is a girl in a yellow dress, a sort of "belle of the ball, and of wanting to have relations with a man that he doesn't like.

A 21-year-old married woman with psoriasis was found to be markedly dependent and immature and suffering from severe insomnia. She resented being a woman. The onset of her psoriasis seemed to be related t the birth of her first child, to the death of her f ther and

to trouble with her husband, who was a gambler and with her mother in-law

A 31-year-old single woman was suffering from a chronic, severe neurodermatitis. Her skin difficulty started at the age of 14, recurred again at 18 and has been present ever since. She described a very discordant love life with a married man who is a pathological liar The affair had gone on for the past 6 years with exacerbations of her dermatitis clearly related to the bickerings with this man and an ultimate breakup She still lives with her mother and feels guilty because of deep feelings of resentment toward her She has a fear of failure which impels her to avoid opportunities she has had to be a success in her work Her psychiatric diagnosis was emotional immaturity with anxiety and dependency reactions.

A 25 year-old Mexican boy with atopic dermatitis and attacks of urticaria which have been lifelong and with recent severe exacerbations was referred to the psychiatric clinic because of a depression which seemed related to the approaching death of a younger brother from a sarcoma and his being forced to take care of another younger brother who was suffering from mongolism. One exacerbation of his dermatitis seemed to be clearly related to an episode in which he became very angry at his gym teacher He claimed that he scratches whenever he is nervous. Both his depression and skin improved markedly with supportive psychotherapy

In the case of a 12 year-old boy with lifelong, chronic generalized eczema, present since the age of 6 months, there was an obvious relation between his getting angry at his older brother and his scratching Otherwise there was no clear-cut, positive psychiatrically significant history This perhaps is more an example of a type of reaction (a passive dependent, obedient personality) associated with a lifelong eczema than of clear-cut emotional factors contributing to the development of his eczema. The brother with whom the patient would get angry had a history of early childhood eczema and a later history of hay fever

In the psychiatric clinic a 27-year-old married woman with atopic dermatitis was found to be suffering from a neurotic personality that was primarily compulsive She gave a history of having received psychiatric help at the age of 17 because of friction with her father which caused her to leave home She developed asthma at the age of 20 while working for her parents, receiving no salary and feeling like a prisoner The asthma has persisted but is not disabling. It improved

after her marriage, which her mother objected to. She had a period of dyspareunia and frigidity lasting for 2 months following her marriage. There was a great deal of discord with her mother on account of the marriage, which led to her not seeing her mother on whom she was quite dependent. The onset of her atopic dermatitis was 1½ months after her marriage. It cleared up with treatment, but she had a recurrence 9 months later a few days after returning home from the hospital after the birth of her first baby Again, her dermatitis was cleared up with treatment, but there was a recurrence a few months later following a severe disagreement with her mother This was the worst attack. The patient recognized that the ups and downs of her skin paralleled the ups and downs of her life. (This still does not explain why the onset occurred after marriage and not before then nor why the skin was affected, not something else)

A 32-year-old divorced woman had suffered from attacks of neurodermatitis on her face, neck, and hands (along with many other emotional and somatic symptoms) since 2 months after her marriage 8 years before. She attributed her skin disease to the difficulty she had with her husband and complained of pains in her head, nervousness, tension, stomach cramps, twitching of the eyes, and excessive salivation. Prior to her first visit to the psychiatric clinic her rash had cleared up considerably she was on a strict diet for allergies (which she resented) in which 22 foods were eliminated. She had received desensitization treatment in the past and had also been treated with Miltown, Thorazine, thyroid nd other drugs before coming to the clinic for treatment. (Physical examination revealed a case of bronchiectasis, for which lobectomy was recommended) Her rash was a minor part of her difficulty though at the time she preferred to consider her current trouble as allergy She itched a great deal even when no rash was present Personal, including sexual, difficulties between herself and her husband had been present from the beginning of their marriage. In fact, she had serious doubts about the advisability of marrying her husband and had made an abortive effort to call off the wedding the day before it was to take place. Her husband was impotent for the first 4 or 5 months of their marriage and when this difficulty was overcome he suffered from premature ejaculations. The patient was incapable of orgasm through intercourse and resorted to masturbation when her husband refused to do it for her She claims she separated from him in 1954 and later di vorced him on the advice of a psychologist she saw at the Institute of Family Relations, though she really didn't wish divorce She became very promiscuous following the separation and felt that she had been tricked by her lawyers into accepting an impossible settlement. She developed resentment

toward all men, who she felt were only interested in her sexually. She continued to wrangle with her husband about the custody of their child, she is suspicious of most people, she has gotten into debt and uses all kinds of rationalizations to keep from going to work. She is having trouble with her son, who is used as the battleground between her and her husband. She can't get along with her father and two younger siblings. She was diagnosed as a hysterical personality with conversion symptoms and psychophysiological disturbances.

A 32 year-old married male with atopic dermatitis, when first seen, was at the tail end of a severe attack during which he "had been tearing himself to pieces. He had had a similar previous attack 2 years before just after he was married. He was obsessed with the idea that he was a coward and admired the type of man who would fight against all odds and take a beating. On several occasions, the patient seems to have gone out of his way to get beaten up in order to prove to himself that he was not afraid. He was by no means a sissy; he had had his share of fights, and on one occasion, when trying to learn how to box, nearly got himself killed" because of an inability to let loose and hit the other man. He was afraid that if he did let loose, the other fellow would kill him. He dates this problem to the age of 11 when, after returning from Europe he reported to school in a little French suit and was unable to deal with the class bully who teased him. He was an only child whose father died when he was 7. His mother was a very aggressive, determined woman who devoted her life to the patient. He resented his mother bitterly, wanted to break away from her but was reluctant to hurt her, realizing that he was all she had. He would be nasty and irritable with her and then feel guilty. For several years following his father's death he moved about considerably with his mother living in hotels, country clubs, and private schools here and abroad. He felt that he was selfish as a result of being spoiled by his mother. He was aware of poor emotional control—he would get angry, sad, and excited too quickly. He tended to put off disagreeable tasks. Like his mother, he was too belligerent, too quick, "tense as piano wire," and overreacted to frustrations. He felt that the world was too much for him and that he was morally rotten and that he didn't deserve to be loved.

The recent severe attack of dermatitis occurred during his wife's pregnancy when he was not having intercourse and when he resorted, at times, with marked feelings of guilt, to masturbating two or three times a day. He tormented himself by "hanging around" a girl in his office to whom he was greatly attracted. He inwardly resented his wife and felt guilty about his lack of consideration for her. He was in great conflict over whether or not to engage in extramarital rela

tions. If he did, he would feel impelled to tell her just as he told his mother everything.

His dermatitis started at the age of 17 on his elbows and neck. H would tear and scratch his skin at night and have to go to school with bandages on. He was at a boarding school at the time. He said to try to stop scratching once he got started was like trying to stop intercourse once it was started. The frenzy was comparable to sexual excitement. He had started masturbation shortly before this and felt very afraid of what it would do to him, as well as very guilty At about the time his dermatitis started, he was having frequent arguments with his mother who at first attempted to make him feel guilty when he was difficult because of all she did for him and then threatened to get married again and leave him to his own devices. At other times she used histrionics and illness to keep him close to her and then criticized him for not being more outgoing with others. From childhood on, he felt, he had been playing the role of a husband, as well as a son, with his mother but feeling incapable of the former He believed that his attitude toward masturbation may have caused his skin trouble and stated that his skin, his guilt, his sexual trouble, his rage, his cowardice, and his mother were all connected.

He has always felt inadequate and that there was something wrong with him. In boyhood, after his father's death, as he and his mother traveled about they slept in the same bedroom, which he felt never looked good. H had repeated incestuous dreams about his mother which filled him with self-disgust, and one of his great fears was that he had an Oedipus complex. His mother always kissed him on the mouth, and he could recall the sensuous feelings he had in adolescence, kissing his mother and holding her very tightly to him. Shortly before the first outbreak of his dermatitis, his mother injured her knee and would have the patient massage it, which would excite him sexually and confuse him.

The feeling of being beaten from the start, which he experienced in relationship to his mother (in great part stemming from feelings of sexual inadequacy) was repeated in relation to others. He didn't feel like man, and his sexual fears were displaced into the sphere of fighting. His concern about cowardice was equated with his concern about his manliness. On one occasion during treatment, he became quite agitated and depressed. He cried and hyperventilated to the point of tetany and, following this, confessed to his mother for the first time how he lacked confidence and how fearful he was. He said about himself "I'm mean, selfish beast inside, and it comes out in my skin. He felt that his skin difficulty was caused mostly by emotional upsets, superimposed on a highly sensitive skin (thin-skinned) He felt very guilty and unworthy because of hostile thoughts toward members

of his family He compared himself to his father whom he remembered as manly strong, successful, and popular (not like the weak boy he felt he was) He had felt the need for a sympathetic, understanding father all his life who would have been able to come between him and his mother while at the same time he was looking for a mother who would take care of all his needs (including sexual) and prevent his being frustrated and enraged. He saw how he looked to his wife to be mother to him while he sought playmates elsewhere His attachment to his mother and his need to please her had made him feel like a sissy in contrast to other boys. He claimed that there never has been a moment when he was free of a fantasy of being in a fight and proving that he was a man—a person to be reckoned with. The psychiatric diagnosis in this case was immaturity reaction with emotional instability

Incidence of Psychocutaneous Disorders

Wittkower and Russell [2] estimated that approximately 45 per cent of over 17 000 patients seen in a dermatologic teaching hospital had conditions in which emotional factors were important, and they felt that it was reasonable to estimate that emotional factors are of significant etiologic importance in between one-quarter and one-half of all skin disease. Table 7 1 shows the types

Table 7 1 PSYCHOSOMATIC DERMATOLOGIC DISORDERS

	Percentage
Total of new patient 17 605	
Abnormal skin sensations (pruritus vulvae pruritus ani, generalized pruritus)	1 4
Skin manifestations	
Acne vulgaris	5 4
Rosacea	1.2
Seborrheic dermatitis	6
Eczema, 13 5% and pompholyx, 2 3%	15 8
Urticaria and angioneurotic edema	5.5
Neurodermatitis 2.4% and prurigo, 1 7%	4.1
Psoriasis	4
Hyperhidrosis and dyshidrosis	0 6
Alopecia areata and universalis	2.3
Lichen planus	0.4
Vitiligo	0.4
Herpes simplex recurrens	0.5
Total	45 2

Source E. Wittkower and B. Russell [ ]

and percentages of dermatologic disorders which they have included in the category of psychosomatic.

Certain dermatologists would exclude some of these from a list of conditions in which emotional factors were believed to be significant (acne vulgaris, seborrheic dermatitis, eczema, pompholyx, psoriasis, herpes) and include others (such as erythema multiforme, stomatitis aphthosa, and burning tongue) Other dermatologists, while agreeing to the presence of emotional factors in acne vulgaris, seborrheic dermatitis, eczema, psoriasis, and herpes simplex, would not include vitiligo, scleroderma, and erythema multiforme among the psychocutaneous disorders. Some of the differences between various workers may be the result of different interpretations of the phrase significant emotional factors. Some authors invariably include trichotillomania, dermatitis artefacta, neurotic excoriations, and delusions concerning the skin among the psychocutaneous disorders. These are clear-cut symptoms of psychiatric disorders and should no more be considered dermatologic than auditory hallucinations should be considered diseases of the ear or a parkinsonian tremor a disease of the hand. At the other end of the scale of disorders considered psychosomatic are those in which psychic disturbances are associated with disfiguring lesions or blemishes. I should prefer to exclude these instances of emotional reaction to existent disease from the present discussion, to avoid confusion.

The conditions which most appropriately fall into the psychocutaneous category (using the restricted definition) are those in which the primary presenting disorder is a dermatologic one in which it is presumed that emotional conflicts via neural, vascular hormonal, or metabolic pathways result in the development of skin lesions (or sensations) or in the aggravation of lesions already existent.

Emotional factors seem to play more primary roles in conditions like pruritus, hyperhidrosis, and in some cases of eczema and urticaria. Whether neurodermatitis or atopic dermatitis belong in this group that is primarily psychogenic cannot be said with certainty at this time Increased sweating that is of emotional origin may contribute to the development of secondary skin

disorders like tinea infections—which then can be considered to have a psychogenic component. In other conditions like psoriasis, acne and herpes, emotional factors even when prominent are generally considered to play more secondary roles.

Incidence of Psychopathology

While we do not yet know what per cent of people without dermatologic disorder show similar degrees of psychopathology as those who do have certain skin diseases, studies have been reported on the incidence of significant psychopathology in patients with skin disorders.

Pruritus Vulvae. There are cases of pruritus vulvae in which no local or metabolic cause can be found. They are usually called idiopathic. Some disagreement exists, but most investigators believe that at least some of these cases are of emotional origin judging from their histories. Wittkower and Russell [2] examined 41 such patients. They found that only 5 of the 41 had as children been on good terms with both parents. More than one-half were critical of their mothers, describing them as domineering, possessive, hard, cruel, selfish, nagging, etc. They were impressed with the high incidence of sibling rivalry feelings of rejection by their mothers, and undue attachment to their fathers (or vice versa) They especially observed that these patients had been difficult children, obstinate, anxious, excitable, etc., and more openly than others admitted interest in their parents sexual relationships.

They found an inordinate amount of psychopathology that varied greatly from patient to patient in this sample, but with an excessive amount of frustration and sexual frigidity The itching and scratching seemed to have both a painful and pleasurable quality and a few patients realized that the rubbing and scratching they did was a form of masturbation—which the authors felt could not in all cases be attributed to the itching The incidence of frigidity was much higher (3 out of 4) in this group of patients than in a small control sample of women (1 out of 10) Two-thirds of the patients were in a state of frustration at the time of onset of the pruritus, 11 out of the 41 had clear-cut psychiatric disorders varying from anxiety states to depressions.

Pruritus Ani. They also studied 25 patients with pruritus ani in whom all local causes were excluded. A characteristic of suspiciousness was commonly found in these patients, and in 11 instances the onset of pruritus was preceded by situations which mobilized or intensified their feelings of persecution. This disorder was twice as common in men as in women and was believed to be related to latent homosexual trends.

Eczema. The rather extensive literature on the personality and emotional factors contributing to the large number of various disorders which have been called eczema (functional dermatoses, localized and generalized types of neurodermatitis of infectious, allergic, or metabolic causes, atopic dermatitis, etc.) is confusing to the psychiatrist as well as to the dermatologist.

Some authors have stressed the sexual origin of the disorder while others have attributed it to such things as tension, feelings of insecurity and inferiority overdependency egocentricity latent aggressiveness, and guilt. Greenhill and Finesinger [3] in comparing 32 patients with atopic dermatitis who had histories of infantile eczema, with normal persons, psychoneurotics, and patients with lupus erythematoses, found a preponderance of obsessive compulsive personalities in the patients with either of the skin disorders and that exacerbations usually were related to episodes of anger or depression.

Kepecs, Rabin, and Robin [4] found hysteric personalities most common in their cases of atopic dermatitis, the characteristic stress in these patients being frustrated heterosexual desires.

Edgell [5] studied 90 patients, military and civilian, with eczema who were compared with a control group consisting of wounded soldiers. He found that eczema patients as a whole differed from the control group in their constitution, childhood environment, general health, and personality development. The differences were most pronounced in the patients who had eczema from childhood and in 50 of the patients in whom there was a clear association between emotional upsets and onset or relapses of their eczema. Emotional disturbances (threats to life, actual or threatened loss of a source of emotional support, blows to self esteem, sexual conflict, anger) were associated with eczematous

eruption in 77 of the 90 patients, and disturbing experiences preceded the onset of the eczema in 46 cases.

Since the civilian patients in the sample were those who were referred by dermatologists because of some behavorial abnormality or failure of usual treatment methods, they cannot be considered representative of all patients with eczema. When just the *military patients with eczema were compared with the more* comparable military control sample of wounded men, the differences described above were not as great. The eczema patients showed a statistically significant higher incidence of eczema or other skin disorder in their families (21 per cent vs. 0 per cent) were more often physically delicate in childhood (43 per cent vs. 4 per cent) more often had other skin and pulmonary disorders in adult life and showed psychoneurotic manifestations (39 per cent vs. 10 per cent) and had sexual difficulties (47 per cent vs. 20 per cent) more often.

Pompholyx. In a study of 50 cases of pompholyx in military personnel, Wittkower and Russell [2] found that four fifths were emotionally maladjusted (30)—i.e. with clear-cut neurotic personalities or symptoms—or overtly psychiatrically ill (10) prior to, or at the time of, onset of the skin difficulty In 33 patients emotional disturbances seemed to precede the onset of the pompholyx

Psoriasis. They also reported their findings on the premorbid personality of 72 unselected military patients with psoriasis 29 were well-adjusted, 29 gave *histories of definite personality deviations*, and 14 were emotionally ill at the time of onset of their skin disorder Emotional factors seemed to play a role in the onset of the disorder in 29 instances (and possibly in 20 others) No comparison was made with a control sample

Seborrheic Dermatitis. Biographical studies were also made of an unselected sample of 100 military patients with seborrheic dermatitis. Fifteen were found to be suffering from clear-cut psychiatric disorders. As a group they were compared with a control sample of 50 wounded soldiers and were found to be more often *inhibited socially unusually conscientious* anxious, unable to relax, and worrisome. However the samples were not entirely

comparable inasmuch as those who were wounded were those who, by virtue of their better adjusted personalities, had attained combat assignment. Those with physical or emotional impairments had been declared unfit for combat and been given other assignments.

However it was found that in 76 out of the 100 patients with seborrheic dermatitis the onset of their skin trouble was preceded by a significant emotional upset, and it was felt that the time relationship between the disturbing event and the onset was such that mere coincidence was unlikely In a like manner emotional factors have been found contributing to various degrees in the onset and recurrences of urticaria, rosacea, acne vulgaris, alopecia, vitiligo, and herpes.

The emotional stresses to which the patients react may seem commonplace and not out of the ordinary to well-adjusted individuals, and doubt may arise about their ability to touch off such pronounced reactions (emotional as well as dermatological) in these patients. However by virtue of their psychic make-ups, these patients are hypersensitive to emotional stresses, which are as specific for each person as antigens are for the allergic patient. The stress may vary from slight inattention on the part of a spouse or conflict with an in-law to sexual rejection, or separation from a source of emotional support. The exaggerated reactions these patients have are very suggestive of the kind seen in children when they are frustrated or feel unloved. Normal young children may more freely express their feelings without shame and guilt. In the process of growing up various mechanisms are brought into play to contain or suppress unacceptable feelings which nevertheless smolder and flare up when stimulated—at times expressing themselves in the skin.

Specific Personality Types

Attempts to define a specific personality type for psychocutaneous disorders will be fruitless. To be sure there are many characteristics which such patients have in common, but they are apt to be those which can be included under the heading of emotional immaturity Such features as exaggerated sensitivity strong feel-

ings of hatred, guilt, shame, sexual frustration, excessive depend ence, chronic tension, feelings of inadequacy constitute the back ground against which the individual's specific combination of wishes, fantasies, and frustrations and conflicts are to be seen. I have yet to see two patients who are alike. Psychoanalysis has given us some general guidelines regarding the course of psychosexual development and clues about how and where difficulties may develop.

Oedipal conflicts may be universal, but each individual resolves the conflict in his own unique way Attempts which have been made thus far to correlate specific personality types or conflicts with specific psychosomatic disorders have been unsuccessful despite reports which appear to indicate the contrary It has not been possible to predict that a given personality will or will not develop a clinically apparent psychosomatic disorder—nor the type of disorder if one is present, from the knowledge of the individual's personality Oral dependence and repressed hostility have been described as the basis of hypertension, peptic ulcer ulcerative colitis eczema, and other psychosomatic disorders, and while this is in the direction of more specificity it implies little more than the term *immaturity*

Undoubtedly constitutional factors (or differences) are present but this does not detract from the importance of psychic factors in the causation or aggravation of skin disorders. We know that obesity is a factor in the occurrence of certain cases of diabetes, even though all obese people do not develop diabetes, nor are all diabetics obese. Much as we would like to explain all diseases by single causes, there are some which at least for the time being can be understood only in terms of multiple causation. This, inci dentally is the case with psychoneurotic disorders which are consistently found to be multidetermined rather than the result of a specific psychic trauma as the movies would have us believe This is presumably the case too, with the psychocutaneous dis orders. Constitutional, local, metabolic, and emotional factors would appear to be involved, with emotional factors playing a primary role in some instances The influence of psychic factors on the onset and course of certain skin diseases is so commonly

observed, as has been the favorable effect of psychotherapy that the existence of a relationship is undeniable.

Because of semantic difficulties and lack of familiarity with each other's basic concepts stemming from high degrees of specialization, dermatologists have difficulty in evaluating psychiatric studies of patients with skin disorders, as psychiatrists do in evaluating reports of dermatologists.

It is important to remember as Macalpine [6] has pointed out, that while psychiatric studies and their findings may not seem to be common sense, they may nevertheless be valid and valuable. People are not always motivated by common sense or logic, and there is much that is irrational in all of us. On the other hand much that has been written on psychocutaneous disorders needs to be examined with a critical eye, since the tendency to oversimplify and to draw invalid conclusions is unfortunately too great in much of the writing in this field.

On the other hand, the mere fact that psychiatric treatment does not help is not proof that a disease is not psychogenic, since many psychiatric treatments are as nonspecific as the dermatologic and as often unsuccessful. Furthermore, many neurotic disorders are so deeply rooted and so pervade a person's personality and mode of adjustment that cure (as with many organic diseases) is not possible.

Macalpine has a word of caution for workers in this field.

> Because psychiatric investigations or explorations are so complex and time-consuming, some investigators have been tempted into using psychological tests in their place. The findings of such investigations are always to be seriously questioned since psychological tests are like any other test—an aid to diagnosis and not diagnoses in themselves. The dynamics that projective tests, like the Rorschach may suggest, cannot be used as the equivalent of the understanding that is obtained of a patient whose personality is explored piece by piece and layer by layer in psychotherapy or psychoanalysis.

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Floyd M. Estess

8

PSYCHIATRIC TREATMENT OF PSYCHOCUTANEOUS DISORDERS

MODERN PSYCHIATRIC TREATMENT marks the development of medicine's rational approach to understanding human nature. Physicians of the past were content to leave the problems of psychic disorders to the priesthood, to the demonologist, magician, or mesmerizer. Of course, the concept of determinism, the idea that events in our universe relate one to the other always occur in causal sequences, etc., was an early tool of physicians. While their explanations for disease were often incorrect, they rested, generally and in so far as somatic disease was concerned, on observations of natural phenomena and theories of natural causation, e.g., the miasma or the cold phlegm. By contrast, those qualities so essentially human, so distinguishing from all other life forms, human mentation and social behavior were seen as supernatural, unrelated to the prosaic substances of reality and akin to gods and devils, spirits and demons. Our humanness belonged to the priest and shaman. This inability of men to turn the attention of their rational selves onto themselves is of interest. At the very least it has cost a long delay in the application of scientific method to the problems of psychiatric illness. It is a

tragic paradox that man's most singular quality his psychic life, has been the last and least studied by the methods so successfully applied to other areas of medical endeavor We can only ascribe this delay to the discomfort men, including physicians and their patients, experience when they try to know their inner nature. This problem of the past lives on today attenuated, receding, but more alive than dead

The last 75 years have brought a concerted, growing effort to understand human thought, feeling, and behavior as natural phenomena, subject to laws, amenable to hypothesis, experiment, and prediction. This scientific effort has led to the classification of psychic disease, to theories of etiology based on rational, naturalistic knowledge, and, finally to systems of treatment proceeding out of diagnosis and cause. This is the way of medicine, modern psychiatry is catching up.

Medical knowledge has changed in other ways. In the last century and early part of this one the systems of Virchow and Koch led us to great successes. No longer however does Koch's bacillus cause tuberculosis—not by itself at least. Rather the presence of a certain number and kind of the acid-fast bacilli taking up residence in a certain kind of individual with a genetic endowment and a whole host of other internal and external characteristics causes clinical tuberculosis We are interested in these other characteristics and may and do study and measure them along dimensions of nutrition, immunology occupation, endocrine function, climate, and many others. In short, medicine has broadened its deterministic base. It has moved on to an understanding of multiple causation of disease

MULTIPLE CAUSATION

The concept of multiple causation—or more correctly the description of cause in different areas of knowledge—for example genetic, chemical, morphological physiological, psychological, or social—provides the rationale for modern therapeutics. Each area of knowledge may offer a point of understanding and of relevant therapeutic intervention in a disease process. So then, each area of knowledge is sometimes useful to the psychiatrist in under

standing and altering pathology of thinking, feeling, and behavior. Our clinical problems often revolve around the identification of this place for effective therapeutic intervention. For example, in tuberculous meningitis, streptomycin seems more relevant than an understanding of the patient's repressed anger. Streptomycin is futile for an acutely depressed tuberculous patient who will not take food, even though streptomycin still kills tubercle bacilli. In this latter case the point of cogent intervention is elsewhere—in the psychic life of the patient, which can be studied, diagnosed, and treated.

These phenomena, the development of rationalism in understanding mental life, the concept of multiple causation, and, finally, a system of therapeutics based on multiple causation, are threads in the historical development of medicine which come together as we consider the psychological treatment of certain disorders of the skin. These are diseases of the organ system most available to our senses. The tangible somatic facts are hardly obscure. Yet, we are told on all sides and can readily observe in the clinic that factors contributing in varying degree to an understanding of such skin diseases can be identified in the psychic functions of patients. Parenthetically, it must be stressed that the recognition of causal factors at the psychological level of scientific observation in no way negates or contradicts the identification of other causal factors in any other area of scientific knowledge—and vice versa. A growing body of clinical experience tells us that what Selye calls the stress of life has to do with the occurrence of redness, eruptions, exfoliation, etc., in the skin of many patients. The request for relevant therapeutic intervention more and more falls not to the dermatologist alone but also to the psychiatrist and increasingly to the psychiatrist's skills as a psychotherapist.

PSYCHOTHERAPY

Psychotherapy is the application by a trained physician of knowledge about human mental functioning to understanding the thinking, feeling, and behavior of a patient for the purpose of altering patterns or arresting morbid changing in the patient's mental life. Psychotherapy is based on the premise that a human

personality is substantially determined by the influence of past and present experiences on a genetic, instinctual endowment. The myriad, complex, infinitely varying sets of experiences which constitute each human life are the things which shape basic drives into patterns of social living. It appears that this shaping of personality has its onset at, or shortly before, birth and occurs with the greatest intensity during the early years. Relationships with other persons on whom the growing child is wholly dependent for life are probably the primary variables for determining future mental functioning.

What human relationship has fashioned, human relationship might change—a bold and, as we shall see, an ambitious idea. Psychotherapy represents a special, structured form of human relationship devised to influence through its several techniques the mental lives of patients.

The decision to use psychotherapy the kind of psychotherapy for what goal, at what frequency with what adjunctive treatments, etc., are all matters which rest on an understanding of the patient's disease Such concepts involve the careful assessment of the structure and patterned functioning of the patient's mental life Characteristic of such an assessment is a careful, detailed history which attempts to investigate not only the usual data of a medical history but *all* that can be learned of the past and present relationships and experiences. The patient's feelings are not ignored in obtaining such information on the contrary it is especially the relationship between feelings and events which concern us. The thoughtful understanding of the patient's sense of anxiety fear rage, panic, and even chaos helps in exploring his problems with a somewhat tentative no touch technique. The physician embarking on psychotherapy is especially concerned for evidences of profound mental illness, for the patient's ability to know more of his own feelings and strivings without panic or disorganization All these things and more must be understood for the physician to make a *basic therapeutic decision. Is this patient able to be* helped by psychotherapy to discover his own motivations, guilts, fears, conflicts, and to understand his neurotic defenses and compromises? Is he able to dissolve by discovery and insight the

sources of his anxiety? Is he capable of emotional growth? Or must an approach be made which bolsters or creates defenses? Perhaps this patient's best hope is to develop mental attributes which protect against awareness of internal chaos. He may need to hide, to push down feelings, wishes, and conflicts which might be shattering to him if exposed. His symptoms may represent the alarm bell for something explosive coming into awareness. Many patients do not have the capacity to know about their own mental life and must be helped, in a manner of speaking, to "not know."

These alternatives, to "dig in" or to cover up, dictate the form of psychotherapy and, in general, lead to decisions regarding goals, frequency and duration of treatment.

The techniques of individual psychotherapy may be considered under three categories: psychoanalysis, intensive, or dynamic, psychotherapy, and supportive psychotherapy.

Psychoanalysis. Psychoanalysis is the most thoroughgoing method for understanding mental functioning. While the term refers to an important theory of human psychology, it is used here to refer to a specific technique of treatment. Psychoanalysis aims at discovering the deepest roots of the individual's needs, frustrations, conflicts, and to expose and decrease his defenses against self-awareness. The mechanics of lying on a couch, saying every thought which enters consciousness, reporting dreams, and the work of free association are all by now "legend" in our culture—reference to the latest issue of any popular magazine will probably supply more details. What seems so humorous to the cartoonists, however, may represent one of the most difficult and emotionally painful courses of action which an individual can voluntarily undertake. For the patient there is only the constant work of exposing his most embarrassing, frightening thoughts and feelings. No detail must escape examination and the effort to find its relationship with all else. In the course of this therapy intense, long hidden feelings and memories of all kinds come into awareness. These feelings are directed at emotionally significant persons such as parents, siblings, spouses, and eventually toward the physician. The development of such intense feelings for the analyst plays a crucial role in the treatment. Through it, archaic,

long forgotten but unconsciously active feeling complexes are brought into awareness and experienced in the relationship with the physician. This, too, you may hear about in the bridge table conversation about the lady who is "in love with" or "just can't stand" her psychoanalyst. In this one relationship, then, the important problems of past relationships may be relived. Now with assistance, they can be experienced consciously, can be tested against reality, understood, and put into perspective. Instead of being unconsciously driven to seek neurotic compromises for conflicting wishes, patients become free to make rational choices. Psychoanalysis ordinarily provides the greatest opportunity for significant, permanent clarification and resolution of conflicts and changes in mental life.

Psychoanalysis is practiced by psychiatrists especially trained in this technique of psychotherapy. It involves frequent treatments, usually four or more times each week for many months. It ordinarily requires the patient to have certain strengths which will allow him to study and become aware of his inner life without undue or uncontrollable anxiety. Not all patients with mental or emotional illness are suitable candidates for this kind of psychotherapy. As yet, psychoanalytic treatment is not recommended for patients who have overt or incipient psychotic disorders. Because of its frequency and duration, this treatment is costly of time and money.

Dynamic Psychotherapy. Akin to psychoanalysis is a form of treatment called intensive, or dynamic, psychotherapy. Usually of less frequency, it ordinarily has more limited goals than psychoanalysis but makes use of similar principles in understanding patients. It, too, may aim at resolving unconscious conflicts. Such psychotherapy may be concerned with primarily one or several aspects of the patient's problems. It is usually less concerned with the deepest origins of conflict and more with the recognition and clarification of conflicts less deeply buried. Most psychotherapy done by psychiatrists is of this type. It may produce important, lasting changes or may help temporarily. It is often most successful during some particularly stressful period of life.

When personality study reveals the presence of severe poten-

tially overwhelming emotional problems in a patient who is without the capacities to discover and overcome his problems, a covering, or so-called supportive, technique is used. Intensive, dynamic psychotherapy may also be put to the service of strengthening abilities to repress, to keep out of awareness, anxieties, and impulses which threaten, somewhat as a dormant volcano, to erupt, torment, or even destroy

Supportive Psychotherapy Supportive psychotherapy is ordinarily on a less frequent basis than psychoanalysis or intensive psychotherapy Occasionally it may be given more frequently Supportive treatment may continue for long periods or be intermittent as needed. Its success is measured by a cessation or lessening in evidence of emotional decompensation. It is often very successful in producing subjective well being—especially in patients with unmet infantile strivings or those who need continuing assistance in testing their thoughts against reality Supportive psychotherapy does not aim at eradicating the sources of anxiety and other symptoms. It helps in defending against anxiety and sometimes in rechanneling the patient's defensive patterns to less incapacitating forms.

Group Psychotherapy Another form of treatment is called group psychotherapy Five to ten patients meet on a regular basis with a psychiatrist. Each member of the group may not only discuss and examine his own feelings but is confronted with his impact on other group members. Through interpretations given by the psychiatrist, patients learn to recognize feelings and behavior patterns characteristic of their relationships with each other The group provides a continuing opportunity for testing out new ways of behaving. Group therapy may be used in conjunction with intensive or supportive individual psychotherapy It is useful for patients who are unable to participate in the more intense one-to-one forms of treatment and especially for patients who have a dearth of relationships in their daily lives.

Patients with psychocutaneous disorders may have many kinds of personality organizations, varying emotional and social conflicts both in kind and severity different degrees of strength, social skill, etc. No one kind or approach to psychotherapy is good

treatment for all cases of neurodermatitis. Each patient must be evaluated for his individual, specific problems and the psychotherapy if indicated, *planned on the basis of rational under*standing. One patient may need, be able to cooperate with, and will benefit from, psychoanalysis or intensive psychotherapy: his skin rash may disappear forever when the sources of his anxiety and stress are clarified. Another patient's rash may be his last ditch defense against a gross schizophrenic regression. To cure his rash, if we could, would not only be bad psychotherapy but bad medicine by any yardstick.

In this regard it is important to take care that in our urge to cure, the magical thinking and acting of our ancestors does not creep back into our dealings with patients and with ourselves. The method of science poses an often embarrassing and even painful and frightening confrontation with the inner nature of man, his greed, lust, and even worse. *Magic can be a comforting,* if temporary, relief if it protects us against such truths. Unfortunately, it also protects us against personal freedom and the realization of our full potentials for gratifying, productive living.

We have discussed the rational approach to patients—an approach based on understanding—on the development of theory, its application and clinical evaluation. Compare this, for example, to the recent revival of hypnosis—a phenomenon which occurs sporadically and, by now, almost predictably. Here there is little concern about why, how, for what purposes, and from what *sources an affliction appears or disappears. The magician physi*cian says "presto-chango" and makes the demon go away. Alas, at times another demon, another symptom takes its place. At times the new symptom is more serious. It must be considered that the removal of symptoms which represent an attempt to solve problems without providing a better or substitute solution may be an open invitation to psychic disaster. No implication is intended for the rational use of *hypnosis, which is, in truth, very limited.* But the promiscuous application of any technique without the careful assessment of the need and possible danger is a violation *of the guiding principles of medicine.* It is doubtful that full strength Whitfield's ointment is good for all skin disease because

it is occasionally good for some; in any case dermatologists would agree that it is essential to know when and why

This brief summation of psychotherapeutic methods, as psychoanalysis, intensive psychotherapy supportive psychotherapy and group psychotherapy represents the clinical application of scientific knowledge garnered at the psychological and social levels of scientific thought. Of growing importance is information about the influence of chemicals on psychic disorder The renaissance of neurophysiology the growth of neurochemistry and related fields seems filled with promise for the discovery of new modes of relevant intervention. As yet, however no new dependably valuable agent or technique is at hand. In spite of high hopes and expectations, the newer so-called tranquilizing drugs are not clearly of any more benefit in neurotic and psychosomatic disorders than other sedatives long known for their helpful but not distinctly curative value. Sedative drugs have a place in the treatment of psychocutaneous disorders. Dermatologists probably have had as much experience in the use of older and the newer compounds as any other specialist. That dermatologists have a continuing interest in understanding more about psychiatric treatment of psychocutaneous disorders cannot be a testimony to the success of tranquilizers. Yet, the hope remains that more specific or more effective compounds will be found, it is likely that they will. The psychiatrist will be concerned at that time, as he is now that when this truly wonder drug is discovered—if it is—physicians not give up the quest for rational understanding of the meaning, causes, sequences, and purposes of an emotionally determined symptom. It is essential to recognize that psychocutaneous disease occurs in a person, that it is interwoven in the most profound and intricate way with the mental life of that person, and that it must be extricated, if it can be, with care.

Frank F Tallman

9

TREATMENT OF PSYCHOCUTANEOUS DISORDERS BY THE DERMATOLOGIST

THE PSYCHOCUTANEOUS RESPONSE to stress from emotional conflict presents the dermatologist with a dual problem how best to treat the discomfort of the lesion and how best to treat the discomfort of the stress. The first has a variety of chemical and electronic answers—answers with which the dermatologist is familiar and with which he works rapidly and comfortably The second is the subject of this material.

The doctor and his patient are the prime reciprocal reactors in the psychotherapeutic method. Thus, in a very real sense the physician as an effective personality is himself a treatment agent His feelings, attitudes, and psychological techniques are treatment agents. To illustrate

A patient demonstrates skin lesions of both wrists extending part way up the forearm. The addition of chemicals to the skin proved ineffective It is obvious that a substantial part of the cause is the patient's own scratching injury to the wrists. The physician pointed this out to the patient rather emphatically "Stop scratching yourself and it will clear up" The patient replied that he was trying [illegible] firm and tart medicine "You just say you are trying. You really aren't!" At this the patient proceeded to scratch his wrists furiously

Here, then, the doctor's medicine was an irritant—rather like turpentine! Another example will illustrate

A chronologically elderly but psychologically young widowed lady took a male boarder Their sleeping quarters were separated by a very thin partition. After about month of this frustrating stress—the boarder obeyed the reality of the partition—the lady developed dermatological lesions in both groins. The dermatologist obtained the above history by being able to listen understandingly to his patient who, by the way said, "Now that I think of it, it's strange that my trouble began soon after Mr X came!" The doctor was able to help the patient understand what her body was saying, and the lesion cleared.

These brief histories serve to illustrate what is meant by the doctor's personality as a treatment agent. In the first case cited, the patient had to defend himself against sharp criticism by a vigorous resort to the identical skin defense that was the presenting symptom. The other patient received treatment by an attentive listening ear and a what-could it mean attitude. We will have more to say later about techniques of treatment and the doctor's role, but now consider in general the patient with psychocutaneous lesions: Here is a person who is miserable with a painful lesion that frequently includes an insistent need to scratch—indeed, perhaps the scratching has come first. Here clearly is a vicious circle, because the produced or intensified lesion is visible evidence that there is a sickness of the body The patient has acquired an abundantly visible answer to the inner psychological turbulence but relative homeostasis is accomplished at a painful price This price adds to the stress, and the circle is complete. A patient of mine once impulsively said, "What would I do without my allergies!" It was a good question for at the time she had no other answer for an intolerable marital situation

Writing in the *Texas Reports on Biology and Medicine* [1] M F Ashley Montagu reminds us that the skin and the nervous system are derived from the same blastocystic ectodermal layer Acknowledging that the skin reflects inner turbulence he points out that evidence indicates that cutaneous stimulation looms as important in supplying a basic need of the developing human being. Tactile stimulation is certainly important during

the nursing months, and being held closely is a recognized need for many many months. J. A. M. Meerloo [3] has written of the skin in its role as a biological defense mechanism. He points out *that the skin is an archaic but effective method of communication*, citing such examples as fear melanosis, goose flesh, and some skin lesions. A short article by Gerald M. Frumess [4] summarizes some of the past bibliography on this subject and is useful for review. As dermatologists you are, therefore, faced by many patients with symptomatology arising from a disturbed physiology and a disturbed psychology. Unfortunately treatment of the *pathology arising from disturbed physiology is only treatment of* part of the disabled person. The program must take into consideration the pathology of the patient's emotional processes, his psychological stresses. Failing this approach the patient is unable to give up his defensive symptom. He has no other answer to his efforts to attain reasonable homeostasis within his energy structure. He may therefore, from the first, unwittingly need to do battle with his dermatologist, a fight which uses the lesion as a battle ground. If the doctor only sees the eruptions and hears only the complaints about them, he has lost a round and perhaps the battle. The patient's conflicts surely prevail. Treatment of the *whole disease, however, has enough encouraging success that it* is gratifying to both patient and doctor and in the end a saving of time and temper to both.

DEPTH OF PSYCHOTHERAPY

Assuming now that the dermatologist has elected to use psychotherapy in treating psychocutaneous disorders, it is necessary that a decision be made concerning the depth of psychotherapy to be undertaken. Psychophysiological symptoms apparently indicate deep-seated conflictual problems whose roots are bedded in the unconscious. To get at this level of personality organization demands training in analytic techniques, a procedure that dermatologists do not either possess or contemplate. The question, therefore, is: Can a dermatologist use mental medicine in his practice? The answer is yes, provided he sets realistic goals, determines the type or types of treatment methods within his

competence and uses those techniques within these frames of reference best calculated to produce results. As pointed out, an exploration of the unconscious requires specialized techniques that go beyond the competence of the dermatologist, unless he is also an analyst, but the more accessible parts of the patient's personality—namely the ego and the superego—can be worked with in a manner calculated to reduce tension and therefore alleviate the patient's presenting symptoms. The object is to strengthen the ego and reduce the corrosive power of the rigid, unyielding, and blindly punitive superego. In patients exhibiting psychocutaneous symptoms the ego is caught between strong primitive and impulsive influences calculated to provide, if successful, instant and complete gratification. Perhaps the need is sexual and loving, perhaps it is destructive and hating. In any event, the ego is put under pressure for action which, though modified by some reality demands, would be, if acted out, at variance with the standards set by the counterforce of the superego (conscience and ideal image). Hence the pressure from below and from above. The dermatologist can strengthen the ego and temper the superego. He cannot give his patient a new ego and a new superego but he can help his patient modify them. The result of this treatment will likely be a reduction or disappearance of the symptoms. The patient's personality will not be cured, but he will be using other defenses less disabling. Even better, he may be mitigating some of the stresses of the past by understanding them better and thus reducing the additive troubles usually acquired through the mechanisms of circular response, i.e., stress from the patient to the environment creates stress in the environment which in turn presses upon the patient. Then there are a variety of stresses that are more immediate and that are particularly disturbing to a weak ego. Consider the emotional impact of stresses arising from acute illness, catastrophe, frustration, and failure, and the like—difficult for everyone but especially so for the weak of ego and the conscience-ridden. A small volume edited by Samuel Liebman called "Stress Situations" [1] is an excellent reference for this type of conflictual situation. These then are the areas of personality to which the dermatologist

should direct his treatment. It is from techniques designed to modify the ego's suffering that he can expect reasonable success.

THE PHYSICIAN

During treatment the patient and the doctor are reacting each upon the other and it is highly important that the doctor have reasonable awareness of his own personality needs and biases, so that he may protect his patient from them. Perhaps the doctor is inclined to like his authoritative role and automatically becomes hostile to a lesion that will not yield to his magic, and thus hostile to its owner None of us like insistent reminders of our failures, and we sometimes have to struggle with ourselves to put up with the patient who somewhat triumphantly says, "See, doctor it's just as bad as ever" Then, too, some of us feel more comfortable if we have people dependent upon us—it makes us feel strong and more secure and well loved Anger at an illness, arguing with the imperfect and weak as a rejection of some hidden personal concern about our own strength, is a factor in our resentment when patients just won't get well. There are among us those who feel best when we are fighting, bloodied, but fighting gallantly against a demon of pathology that will not yield. Some of us might collapse if the enemy gave in too quickly! Then there is the doctor who gets disturbed if his patients are critical either in attitude or words. He feels hurt, and this brings its inevitable anger and that in turn somehow creates the feeling that it's the patient's mean perversity that is the trouble It is indeed too easy for the doctor to become accustomed to thinking of his patients in terms of their symptom complex rather than as people with disease.

There are obviously other needs and attitudes that are our own, that "treat our patients for good or for ill It is suggested that the doctor accept the fact that alone he cannot radically change himself but he can and should think about his personality and its effect upon his patients. He can and should consciously modify as best he can his attitudes when they appear to be using the patient's problems as an answer to his own obvious needs. To illustrate with another example

A patient complained that a certain prescription was not helping. Her doctor said: Just keep using it. Do as I tell you and don t argue. Apparently this man was uncomfortable when his uthority was questioned.

THE PATIENT

In considering the patient in the doctor patient relationship we can start with the knowledge that the patient will have similar if exaggerated attitudes and needs. There are dependent patients, hostile ones, demanding, pleading, weeping, lost, withdrawn, sexually infantile, defeated, and the guilt ridden Always, too the symptom complex tries to answer several conflicts Thus, unfor tunately the presenting problem is many-faceted. We postulate that anger guilt, infantile dependency needs, and erotic desires are all present in some degree and that the patient has not found a mature and satisfactory way of handling those feelings. Also, he has failed to find a purely psychological answer such as compulsive-obsessive reactions. The psychocutaneous symptom has become an answer not a well-adjusted one but still an attempt at homeostasis. Many workers in this field have concluded that psy chocutaneous lesions in the main are expressions of hostile, aggressive impulses and feelings. Milton L. Miller [5, 6] Greenhill and Finesinger [7] P F D Seitz [8, 9] and Seitz and Gosman [10] all express this opinion. However Menninger [11] thought that excoriative forms of dermatitis were an evidence of the death instinct acting as an attenuated attack upon the body Seitz and Shipley [12] writing in an interesting communication, suggest that there is an element of the voluptuous and exciting, namely an erotic component in patients exhibiting a psychogenic pruritis and neurotic excoriations. Those who follow the literature will find a variety of opinions concerning the cause and specificity of psychocutaneous disorders. This means that there is still much to learn through research The research of John Lacey and associates [13] reported in *Psychosomatic Medicine* suggests that perhaps what we are seeing in some patients is a reaction to stress that is for them a specific biological characteristic i e any stress acting through the autonomic nervous system tends to be evident i the cutaneous structure In others, the lesion may be

symbolic pruritus vulvae may be both an erotic experience and a punishment at the same time; or again, the stress may give the patient a "right to scratch," as one patient put it. Or a lesion, as in the elderly lady cited earlier may be both a punishment for and a symbolic expression of, an unsatisfied and conflictual urge. In any event, the doctor's task is to help the patient help himself But how? Armed with an awareness of the patient as an emotionally reacting person and fortified with some understanding of himself, we are now in a position to discuss methodology Levine, in his book "Psychotherapy in Medical Practice" [14] lists many items appropriate to the therapeutic armamentarium of the dermatologist, but time and space do not permit us to discuss them all here. However we will discuss several methods in the hope that it will stimulate the reader to further consideration of this important subject.

THERAPEUTIC APPROACH

What are the most reasonable tools? Time is the first and almost paramount. Many doctors will, at first, be sure they do not have the time to work psychotherapeutically with their patients, but experience will show that difficult patients will use up much more time in a useless and endless merry-go-round of frustration, having consumed much more time than would be necessary to do a satisfactory psychotherapeutic job Many of us use time as an excuse and as a shield to protect us from the patient's feelings. With psychocutaneous patients we have to be secure enough to lower it a little

Now that an appointment of at least 45 minutes has been set aside for a beginning, what next?

Before discussing specific psychotherapeutic procedures we need to consider some more general approaches that are essential. First, explain to the patient in layman's language that stress and conflict are involved in the illness, that medication alone is not enough, and that stress can be mitigated by talking it out and by getting help in understanding the relationship of people and events that precipitate quantities of stress that are not being managed by psychological means—hence the body's attempt to

bring about balance, albeit an uneasy and uncomfortable one. Undoubtedly the patient will want to discuss this concept and will have questions to ask concerning frequency of appointments and length of the treatment program. One visit per week lasting about 45 or 50 minutes will be found to be ample and safe in most cases. When it is found that time is lost because much of each visit is used by the patient reciting everyday events (a defense in itself) visits will need to be increased temporarily to two per week. More frequent psychotherapeutic visits than this are likely to involve doctor and patient in a relationship that may result in the patient's becoming so extremely dependent upon the doctor that such ego defenses as the patient has are weakened rather than strengthened. In short, too frequent appointments may well do more harm than good.

Of paramount importance to good therapy is the art of good listening. It would not seem difficult to be quiet and while quiet listen and observe, only speaking for a definite, considered reason, but it is! We doctors are taught early in our careers to ask pointed questions—to get information from our patients by *taking* a history In psychotherapy we wait for the patient to *give* us his history in his own time and in his own way and with his choice of divergence. One doctor said, when discussing this difficult role, "It's like following a cow about in a pasture. I can hardly stand it, but when I tried to get the patient to keep on the subject, she dried up—stopped talking. The reason for listening is to enable the patient unwittingly to move closer and closer to the problems that he consciously knows and either finds too painful to face directly or perhaps fails to realize the importance of at first.

It is undeniably difficult to permit patients to change the subject at will, but to expect order in the patient's own presentations of themselves is to expect a degree of automation inconsistent with psychotherapy

As the patient talks, observe nonverbal types of tension—flushing of the face mottling of the neck, restlessness of body picking at nails, clasping or unclasping hands, increased facial or axillary perspiration, throbbing pulse as seen in the neck or perhaps a

rigidity of posture as if the patient were holding himself together by the use of every voluntary muscle.

QUESTIONS DURING EARLY INTERVIEWS

There are, however a few questions that need to be introduced during the earlier interviews. Perhaps the most important one concerns the relationship between stress and symptoms. For example "What pressures or stress happened to you shortly before your skin trouble began?" The patient may very well respond by denying everything unusual, but nevertheless the doctor should suggest that events connected with feeling should be reviewed in case something inadvertently was overlooked. Listening is difficult, but therapeutic talking is no less so Brian Bird has written an insightful and helpful monograph about this skill. It is called "Talking with Patients [15]

The book stresses the importance of having a definite purpose in mind and deals with a number of specific situations or crises in the life of the patient that require a psychotherapeutic attitude as an emergency measure

Continuing psychotherapy is, however not a crisis matter and here the emphasis is on listening rather than talking

A patient with a severe facial psychocutaneous lesion, when asked concerning his preceding history noted that his trouble began shortly after a strenuous staff meeting during which the functioning of his department had been criticized. After talking about this he said, Funny I hadn't thought of this before—my face sure was red and it still is!" This patient had been working under severe pressure for months and had become angry at several persons and at himself for being angry His mother had been a peace-at-any-price person, and he had acquired a feeling that to be angry as practically a sin and therefore cause of enormous guilt.

It is important, too to investigate the relationship of surrounding circumstances to the lesions—as, what makes the patient's skin feel the worst?

A patient, in response to this, recalled that her trouble seemed worse when a neighbor to whom she felt in conflict, called. Said she "When Ann A. comes I like to look my best. She is so lovely But no I be

to call her attention to my skin by scratching furiously. It's embarrassing and maddening! She is so perfect!"

Just as it is important to let patients set their own pace and direction, it is necessary to help them when it seems apparent that they are struggling with an emotion that is in danger of becoming overwhelming. Then one should suggest that the matter be discussed later and immediately follow with a comment designed to change direction and thus let the patient regain his defenses. Relieving tension by ventilation is somewhat akin to draining off fluid from a body cavity—it has to be gradual to avoid dangerous shock.

Avoid being put in a position of being judge advocate or partisan. Patients are always trying to bolster their ego, add to their punishment, satisfy dependency needs by making demands upon their doctor for advice and opinions. Being aware of these underlying but nevertheless ever present maneuvers one can use them to help patients understand their problems. This is the proper course. To be unwary is to be enslaved!

When a patient says, "What would you do, doctor?" or "How should I describe this?" the trap is set. To avoid the snap and to help the patient deal with his own feelings, the proper response is "Talk some more about it—perhaps you will find your own answer to the problem. Occasionally patients will persist in trying to get an edict handed down from Olympus, and the doctor will then have to say: "What I would do or advise is really beside the point, because I'm not you, and therefore my decision might well be alien and arbitrary if carried out in your life. Perhaps you are asking these questions to be sure I'm interested in your problems, or maybe you feel a need to have someone share the responsibility of decision with you in case it's not a good one. You could, of course, be dodging the issue These suggested comments may not be appropriate to a case in point but are offered only as examples of an attitude consistent with the doctor's role in the treatment program.

DURATION OF TREATMENT

Now some comments about duration of treatment. Generally speaking, results should appear within 5 or 6 months of weekly interviews. If the patient is not improved by then, the indications are that the psychocutaneous lesions are a very important defense which the patient cannot either give up or substitute with a less disabling mechanism. The case should be reviewed with the patient and, where possible, a referral made to a psychiatrist or to some available psychiatric facility. If this is not possible, regular but less frequent visits will likely keep the condition from deteriorating and over a period of time may well improve it. This is because reaction to therapy proceeds between interviews and after they have stopped, because the personality goes on assimilating new insights and thus gains better defenses.

Patients should not be encouraged to discuss dreams, nor should the doctor attempt to interpret them. Neither should he try to interpret the relationship that exists between patient and doctor, i.e., in psychiatric language, the transference and counter transference. Avoid too the technique of free association, because this and the aforementioned techniques are difficult and complicated areas properly reserved for specialists in psychiatry.

Some patients with psychophysiological disturbances who are "decompressed" too quickly are sometimes likely to develop acute anxiety attacks which end very often in their failure to keep their next appointment. This is unfortunate but not critical. With others the abrupt removal of defenses may release suicidal feelings that will overwhelm the patient, who may well respond by committing suicide or making an attempt. This sad state of affairs can be avoided by certain precautionary measures. First, let the patient do the talking and be scrupulously sparing with interpretations. The rationale in this frame of reference is that patients, if left to themselves, will protect themselves against a calamitous dissipation of defenses. Second, when the patient seems unduly upset and still goes on with the disturbing material, change direction by deliberately introducing another idea as "We will talk about that some time later. How about. . . ." The patient will come

back to the painful subject again, but perhaps not for several weeks. Third, watch for expressions of hopelessness as applied to the person himself as "I m utterly worthless I feel nothing inside —it is as though I were empty or dead, or "I've lost interest in how others feel; nothing seems to exist that I can feel about around me; days of emptiness follow one after the other or "Life is not worthwhile. Expressions like these, coupled with evidence that the patient is withdrawing from human as well as material contacts, are ominous symptoms, and certainly for the patient's safety proper steps for supervised attention and a psychiatric consultation are mandatory

We have covered very briefly but within the limits of presently available time, some general psychotherapeutic approaches to psychocutaneous problems.

INTERPRETATION

To be considered now are some more specific methods that are appropriate to utilize. Note that so far the role of the physician has been very passive. The patient has been well supported by having an opportunity to ventilate—good treatment, but not enough. Comment has been made about interpretations that the doctor makes on the basis of these productions, insight that in time the patient would very likely reach himself but with the limited contact in this type of doctor patient relationship, occasional helpful comments are necessary To illustrate

A patient 18 years old had a very bad case of acne vulgaris that was being made worse by picking and scratching. The patient went East to school, followed his dermatologist's directions regarding diet, used a prescribed lotion, and the condition cleared. During a short visit home the skin became almost immediately worse. The doctor asked the patient if he could think of any reason why his acne should be so much worse and suggested that the answer might have to do with stress. The patient said that home was the same. The doctor said, "The same?" The patient said "Yes, when I come home, my stepfather gets upset and nags t me constantly I can hardly hold my temper!" The doctor said, by way of interpretation, "Do you think it possible that the anger that you hold back could hav anything to do with your face?" The student said, "I don't know about that, but he makes me sweat trying to hold on to myself As time went on the dermatol-

ogist made the point that the feeling about the stepfather added enough strain to increase the acne and that likely the patient was scratching his own face as a substitute for that of his stepfather

Here we see interpretations being used to give the patient in sight into the interpersonal relationship that was certainly additive to his skin lesions.

SUGGESTION

Persuasion and suggestion is a common psychotherapeutic tool. Used in a general sense and alone they are fleeting and ineffective techniques. However suggestions in the sense that the doctor is consistent, pleasantly firm, and knowledgeful in his handling of the patient's problems is a strong suggestion to the patient that these attitudes and opinions are worth accepting. In this situation the patient will react consciously by accepting a greater authority Unconsciously too he will accept the suggestions if he feels a positive interpersonal relationship with his doctor So, therefore there is a place for persuasive suggestions, but there must be additive factors because alone an accepted suggestion is fleeting indeed.

REASSURANCE

Reassurance is another specific method that in stark outline leaves much to be desired. Many patients have been told, "Your problem is not serious the skin will clear don't worry! This is often a strong but very temporary dose of psychological aspirin unless its use comes after understanding the patient's problems and follows new insights that the patient has been helped to gain For example

A lovely 22 year-old girl married a solemn, rather boring but solidly successful man of 38 After 3 years of his d ll solidity the patient began to develop a dry eczematous condition of both hands to the wrists and both feet to the ankles. Her dermatologist decided that the condition involved a psychological factor and began to study her from this point of view

In therapeutic interviews the patient gradually began to express her anger at her husband and her conflict about this feeling. True he was a good kind, steady and utterly predictable individual, but how

stultifying to be with! When she said, "Sometimes I could choke him, but I'm ashamed to feel this way and to say it even to you is disloyal, the doctor was able to point out the connection between this conflict and her hands and was able to reassure her concerning the matter. He could point out that everyone has habits that are annoying and that it is better to recognize them and work out a method calculated to bring about some changes in the situation. Anger at the husband—suppressed—was not constructive. Ranting at him in an uncontrolled way would not help. But working out a plan to improve the relationship between them would be constructive.

ENVIRONMENTAL MANIPULATION

This point brings us to another technique—environmental change or manipulation in the case above, improvement of social living. This patient, upon the advice of her dermatologist, began to arrange to have guests for evenings and dinners. She planned week-end trips and occasional trips to the theater etc. All this was done gradually and with moderate doses. One day her husband remarked that it was wonderful to have someone who cared enough to see that I have some fun. In the same case, the patient also took on daytime activities that interested her. Here we see a definite plan as part of a reassuring attitude. Just saying, "You'll be all right, with nothing more not only would have been useless, but its failure would most certainly have added to the patient's stress.

We have postulated that psychocutaneous skin disease has, as a causative component, emotional stresses that the person himself is unable to contain appropriately or to dissipate profitably or failing this, he is unable to drain off their psychological symptoms. Skin lesions have been the answer.

We postulate that external medication will be more effective if the conflictual lesion is treated concurrently and in some cases external medicine is entirely ineffective unless accompanied by attention to the stress-producing problem. Wittkower and Russell [16] in their book Emotional Factors in Skin Diseases elaborate this concept, and the monograph will be found rewarding.

Psychotherapeutic treatment agents can and should be used by the dermatologist with certain safeguards. Referral to a psychia

conflict, thus insuring better solution of environmental conflicts. *Psychocutaneous lesions will often yield to the dermatologist who uses psychotherapy in his treatment program.* The removal of excessive emotional stress is an important treatment goal. Many and perhaps most dermatologists use psychotherapy *in one form or other and few of the concepts discussed here are new to them.* Nevertheless, the *sine qua non* of successful psychotherapy is the organized and consistent uses of these technical tools according to the special needs of the individual patient. A diagnosis of psychocutaneous skin disease implies the use of this treatment as basic to any other

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Walter B Shelley

10

SEBORRHEIC DERMATITIS

SEBORRHEIC DERMATITIS is a chronic scaling inflammatory eruption in which the localization is the remarkable distinctive feature. It is the location of the lesions, rather than their clinical or microscopic appearance, which sets seborrheic dermatitis apart as a true entity Certainly we cannot culture or demonstrate any infectious or allergic causative agent. Despite the implications of the name, none of the epidermal appendages shows a unique change. It is not even a remarkable eczema either clinically or histologically But always the localization stands as the singular feature.

DISTRIBUTION

What is this distribution pattern? Figure 10-1 points up the essential topography viz., all the areas rich in sebaceous glands and all the intertriginous sites. The eruption may appear in any one or more of the areas given in the list on the next page

These sites show a symmetrical bilateral involvement and are known as the seborrheic areas Indeed, any scaling or erythematous eruption in one of these seborrheic sites must first excite a

References 1–8 carefully survey the entire field and detail modern concepts and therapy

diagnostic suspicion of seborrheic dermatitis. The area is such a remarkable determinant that one may be lulled into a false diagnostic security with that most common of all seborrheic afflictions, dandruff. Scaling on the scalp spells dandruff to patient and physician. Yet, one must be alert to the possibility of other problems such as fungous infection.

Scalp	Axilla
Forehead	Inframammary
Eyebrows	Periumbilical
Eyelids	Suprapubic
Nose-cheeks	Groin
Nasolabial folds	Gluteal cleft
Ear canal	Perianal
Retroauricular area	Vulva
Presternal area	Glans penis–coronal sulcus
Interscapular area	Skin folds

Seborrheic dermatitis has many clinical masks, but a unifying and underlying pattern usually can be perceived. Generally seborrheic patients have a glistening, shining, oily skin with patulous follicles. This is most dramatic on the face where the sebaceous glands reach their maximum development in all individuals. *Seborrhea* is the term which describes this hypersecretion of sebum. Seborrhea is not seborrheic dermatitis any more than hyperhidrosis is a form of miliaria. Furthermore, seborrhea is not an invariable, but certainly a common, concomitant of seborrheic dermatitis. Seborrhea corresponds to hyperhidrosis and actually the two often coexist. Seborrhea indicates an excessive production and flow of sebum, and the semanticist who wishes for precision to prefix *hyper* or *oligo*- should be referred to the term diarrhea. Although the presence of seborrhea does not result in seborrheic dermatitis, and the diagnosis of seborrheic dermatitis does not demand a seborrhea, the presence of oily skin is a typical finding. We have recently reviewed the physiology of the sebaceous gland in normal skin, and it is pertinent to review some of the findings here [9, 10]. The sebaceous gland is not under direct neural control but rather is a holocrine organ constantly manufacturing sebum at a continuous, relatively con-

stant rate. The size and number of the glands determines the output. Our data indicate that the quantity of sebum produced is in no way affected by the amount of surface fat. Sebaceous glands are richest on the scalp and forehead, next most abundant on the chest and back, axilla, and groin, and least common on the arms and legs. Sebaceous glands are not present on the palms or soles. A most important correlate of sebaceous gland activity and seborrheic dermatitis is found in the fact that seborrhea and seborrheic dermatitis are common in infancy rare in childhood, and common again in puberty and adult life. Certainly endocrine

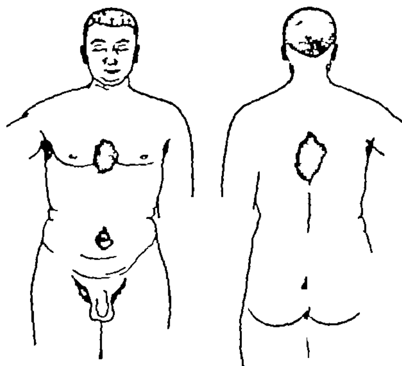


Fig. 10-1. Distribution pattern of seborrheic dermatitis. This topography is unique for seborrheic dermatitis.

influences are of considerable importance. As yet the details of this hormonal control are not entirely clear

CLINICAL FEATURES

To return to the clinical picture seborrheic dermatitis is basically a mild inflammatory process. Histologically one may see evidence of nonspecific inflammatory change in the dermis, as well as epidermis. It is not a striking pattern. Clinically the mildest forms are grossly noninflammatory although the scaling one sees is a consequence of the microinflammatory change.

Simple scaling of the scalp (pityriasis simplex capitis, or dandruff) is at once the mildest and most common of all of the types of seborrheic dermatitis It is known to all as the fine furfuraceous white scaling so apparent on the man in the blue suit. It is associated with *seborrhea, which may manifest itself under the loupe* as glistening oil droplets at the follicular orifices. Furthermore, this seborrhea can be demonstrated by application of a clean glass slide or cigarette paper to the scalp. The excess sebum becomes very evident with this simple testing. The patient may complain of a dry scalp paradoxically but this may be the effect of a change in the surface of the hair Altered keratinization may manifest itself as an actual roughening of the hair cuticle. Itching is common in dandruff yet elsewhere seborrheic dermatitis may be symptomless. The question of alopecia is repeatedly under consideration. I feel that alopecia may occur in association with seborrheic dermatitis but that it results from the hormonal changes responsible for the seborrhea rather than from the dermatitis. Certainly severe eczema and psoriasis do not cause loss of hair

The scalp may show a grossly inflammatory form of seborrheic dermatitis. Here, circinate circumscribed, erythematous, scaling lesions appear or the entire scalp may be involved with extensions out beyond the hairline as a corona or fringe of scaling erythematous skin. Yellowish matted crusts develop at times, and serous *exudation may become prominent.*

On the face seborrheic dermatitis appears as patches of scaling and erythematous plaques. The forehead, the bridge of the nose

and adjoining cheeks, as well as the nasolabial folds are commonly affected. Seborrheic blepharitis is another variant. Here the lid margins are scaly reddened, and at times crusted and edematous. In the ears, the canal may be very pruritic, scaling, or crusted. The retroauricular area often shows fissuring, exudation, and frank secondary bacterial infection. On the chest in pityriasis corporis (flannel rash) multiple discrete, circinate,



Fig. 10-2. Typical seborrheic dermatitis of face, characterized by erythematous scaling areas of forehead, nose chin.

scaling, yellowish areas are seen in the midline, both in front and in back. Some patches in the presternal and interscapular regions represent the minimal involvement. The pubic area may also show crusted scaling as the scalp. It must always be recalled that seborrheic dermatitis may underlie any otitis externa or pruritus ani.



Fig. 10-3. Typical seborrheic dermatitis of external ear. This may be extremely pruritic. Topical hydrocortisone preparations are remarkably effective.

A major form of seborrheic dermatitis is the flexural type. This may involve any and all folds of the body. It simulates intertrigo and indeed may be indistinguishable in the absence of other localizing evidence of seborrheic dermatitis. The inflammatory exudative and secondary bacterial element here is predominant. Scaling may not be seen except in satellite plaques or in the marginal areas. Fissures may be prominent. It is important to note that the axillae, groin, gluteal cleft, and inframammary folds are common sites of involvement. Rarely seborrheic dermatitis may become severe and generalized, resulting in a generalized exfoliative dermatitis with no diagnostic clues remaining except the history.

In children, *exfoliative dermatitis of seborrheic origin* has been termed Leiner's disease. It is rare and demands general pediatric hospital care as well as dermatologic attention. Secondary bacterial infection, protein losses, and heat regulation each pose serious problems.

The course of most seborrheic dermatitis is chronic and relapsing. Dandruff demands the continual long-term type of therapeutic attention that is associated with dental hygiene. It is not enough to say the scalp is now clear of scales. They will commonly return within a few weeks. The acute inflammatory element can be controlled and eliminated, but the diathesis cannot.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis [4] includes a careful consideration of other forms of eczema. *Eczematous contact dermatitis* can certainly mimic seborrheic dermatitis. On the scalp one must consider reactions to hair dressings, tonics, shampoos, sets, and chemicals used in permanents. In the flexures, deodorants, antiperspirants, clothes, topical medication, and frames for glasses all come under consideration. In infancy seborrheic and atopic dermatitis are very hard to sort; some patients developing a seborrheic dermatitis early which later becomes a classic atopic patterning. In adults the presence of lichenification eliminates seborrheic dermatitis. Impetigo may pose a differential problem, and actual bacterial infection of seborrheic dermatitis may make

the distinction academic. Ichthyosis is far more widespread than seborrheic dermatitis. Both lupus erythematosus and seborrheic dermatitis may involve the bridge of the nose and the cheeks. Careful clinical study and biopsy may be needed to distinguish these two.

Psoriasis has been viewed by some as a congener of seborrheic dermatitis. Many examples of a fusion of syndromes are seen. We view the seborrheic dermatitis as exciting Koebner's phenomenon so that one does see psoriasis developing in seborrheic patches, whether they be on the scalp, face, chest, or flexural areas. The scaling becomes typical of that of psoriasis, but the localization remains that of seborrheic dermatitis. This is the seborrhiasis or seborrheic psoriasis [11]. Fungous infections may closely simulate any form of seborrheic dermatitis so that appropriate laboratory (Wood light, scrapings, and cultural studies) may be necessary. Pityriasis rosea is clinically suggestive at times, but the cleavage line distribution, the collarette of scales, and the herald plaque each aid in distinction. Intertrigo of simple bacterial origin is always to be considered in the study of the flexural types of seborrheic dermatitis. On the face chronic discoid or acute disseminate lupus erythematosus may enter into the differential diagnosis. Frequently the biopsy is decisive, since lupus erythematosus presents a distinctive patterning.

Photosensitivity reactions on the face may closely resemble seborrheic dermatitis. In fact, some observers have described a light-sensitive seborrheid which appears as a result of sunlight exposure [12]. Finally, drug reactions must always be considered. Gold, arsenic, Atabrine, barbiturates, and other compounds may each produce a seborrheic drug reaction. Failure to recognize this may result from a poor history!

CONTRIBUTING FACTORS

No single cause of seborrheic dermatitis is known. Certainly a number of significant factors are operative. The most noteworthy is individual susceptibility. This diathesis is seen in many dermatologic conditions and really reflects certain unknown yet critical constitutional traits. We have learned of the atopic diath-

esis, of the psoriatic diathesis, and indeed the miliarial diathesis. This individual susceptibility is remarkable, since many older patients with seborrheic dermatitis can give a history of cradle cap and otitis externa in infancy greasy skin, blepharitis, and dandruff in the teens, and recurrent attacks of intertrigo of the axillae and groins as adults. These are individuals who show repeated manifestations of their seborrheic diathesis. The English race is peculiarly susceptible to seborrheic dermatitis. The history of a familial seborrheic trait is also obtainable from time to time, pointing up the hereditable features. In the mildest form, dandruff, the dermatitis, is so common as to be viewed by some as physiologic. In this there is an analogy with acne. Certainly the hormonal pattern influences the course of the eruption [13-15] Seborrheic dermatitis is not seen in eunuchs, yet testosterone will induce it. The prepuberal years are largely free of seborrheic dermatitis, yet in infancy seborrheic dermatitis of the scalp may be prominent. We suspect that maternal hormonal influences are still present in these patients in the first few months of life, thus accounting for the infantile seborrheic dermatitis and also acne. Furthermore, it has been shown that estrogens (pellet implantation) will reduce all the manifestations of seborrheic dermatitis. Seborrhea, dandruff, and other seborrheic changes all show a remarkable involution under very high estrogen dosage. A third causative factor of considerable importance is that of surface microflora. Undoubtedly much inflammatory change in seborrheic dermatitis results from a reaction (direct or indirect) to the surface bacteria. The oil and sweat of the classical seborrheic skin all promote enormous overgrowth of the bacterial population, since desiccation is the prime degerming mechanism. These bacteria often produce an actual superficial pyoderma, but the transition is so subtle as to defy ready clinical distinction. We feel, however that the oozing crusted seborrheic dermatitis is invariably an infected skin (Fig. 10-4) These patients appear to have periodic diminution in their resistance to this infection. Many attribute this to fatigue and/or tension.

The surface skin fat and the bacterial flora are not invariably increased [16] It would appear that the sebaceous gland response

to hormonal stimulation is commonly parallel to, but actually independent of, the inflammatory response. Again the bacterial count and sebum secretory rate bear no absolute relationship. One final point refers to a recent study [17] of the chemical nature of the surface fat in seborrheic dermatitis. This fat was found to have a lower squalene and higher cholesterol content than nor



Fig. 10-4. Secondary bacterial infection complicating seborrheic dermatitis of the ear. Compresses and *Neo-Cortef* ointment are effective in treating this.

mal. It is not possible to say whether these changes record a cause or an effect of seborrheic dermatitis.

Special causative trigger factors are drugs and sunlight, but these are operative only in the rare or unusual example. Poor hygiene, that is, *failure to wash the skin promotes dermatitis* by allowing sebum, bacteria, and bacterial metabolic products to accumulate. Some observers feel that failure to exercise is also *harmful. Others deplore the high carbohydrate diet,* foci of infection, and excessive environmental heat. Certainly bacterial infection of the dermatitic areas may supervene as a result of spread of organisms from the infected nasopharynx. Staphylococci as well as hemolytic streptococci play a significant role in this regard.

Pityrosporum ovale is not the cause of dandruff or any other form of seborrheic dermatitis [18 19] Two great dermatologists, Unna and Sabouraud, launched this infectious nature theory and with the aid of commercial advertisements it has remained in full vigor to the present. It is true that the bottle bacillus (*P ovale*) grows in great numbers in all seborrheic areas, yet this is purely a manifestation of the lipophilic nature of this organism. No one has any significant evidence that the pityrosporum is other than a completely harmless nonpathogenic saprophyte.

The emotional factors in seborrheic dermatitis have been studied by a number of observers [20 21] There is evidence that emotional stress may indirectly activate the disease However this disease is certainly not of psychic cause, and it is possible that the psychic factors operate through the hormonal glands. The personality traits of the seborrheic have received attention. Despite the fact that some patients with this disease may show neurotic traits and symptoms many observers feel that there is no distinctive personality deviation

Controlled observations have been made on two striking examples of seborrheic dermatitis arising from known causes. Vilter et al. [22] have actually been able to produce seborrheic dermatitis experimentally These observers saw oily scaling erythematous lesions develop in the scalp, eyebrow nasolabial folds and retroauricular regions in the majority of subjects who received

150 mg of deoxypyridoxine while on a vitamin B complex–poor diet. Deoxypyridoxine is a vitamin B_6 antagonist and these studies suggest that patients with seborrheic dermatitis may have a metabolic defect in pyridoxine metabolism. The eruption rapidly disappeared when pyridoxine was added to the diet or applied locally as a 1% pyridoxine ointment (four times daily water soluble base) In clinical seborrheic dermatitis the addition of as much as 300 mg of pyridoxine a day was without effect, but topical pyridoxine ointment was helpful. Furthermore, application of 10% deoxypyridoxine ointment caused local flaring of clinical seborrheic dermatitis lesions. We can conclude that the pyridoxine deficiency seborrheic dermatitis differs from the clinical version, yet further study is indicated. Riboflavin deficiency [23, 24] has also been shown in some subjects to lead to the appearance of seborrheic dermatitis. Cure of these experimentally induced changes was rapidly effected with riboflavin added to the diet. In a second study of interest, Bettley and Martin described a unilateral seborrheic dermatitis of the face following a nerve lesion [25] They found both seborrhea and an increased number of bacteria in the affected area. They suggested that a unilateral brain stem lesion could be responsible, since no evidence exists to show that peripheral nerve injury is followed by seborrhea or seborrheic dermatitis.

TREATMENT

The treatment of seborrheic dermatitis varies enormously from the cure of cradle cap with a shampoo to the heroic attack on a generalized exfoliative dermatitis with corticosteroids and hospitalization [26–33] There is no specific cure or indeed specific treatment. Nevertheless, much can be done. We have elected to review the current therapy under several appropriate headings.

General Measures

The three R's of an antiseborrheic routine are Rest, Reassurance and Recreation. Many of these patients have developed chronic fatigue from overwork, and attention must be directed to the importance of the simple rules of hygiene For some a

bacterial infection becomes evident. Serous oozing and matting of the scalp is a common manifestation of secondary pyoderma. Another site for severe streptococcic and staphylococcic infection is the intertriginous area. Systemic antibiotics are of unquestioned usefulness in these severe bacterial episodes. Erythromycin in a dosage of 250 mg four times a day is a common drug of choice. Resistant strains may be grown and typed for sensitivity. Novobiocin and chloramphenical-sensitive pathogens are found at times. Antibiotic therapy once undertaken should be continued in full dosage for at least 5 days. It may be stopped abruptly at the end of this time, or the patient may continue for a short period with a maintenance dosage of a single capsule a day.

Hormone therapy has been disappointing since at present we lack specific antihormonal agents. Androgens appear to be basically responsible for much of seborrheic dermatitis. Yet we have no drugs, including the estrogens, which neutralize the effects of androgen.

Tranquilizing drugs have given emotional calm to many anxious patients, and they have a role to play in this area in the treatment of the emotional stresses and strains which may operate to initiate or accentuate seborrheic dermatitis. Thorazine may be prescribed in a dosage of 50 mg at bedtime and as required one to three times in the day.

Finally, we have had some success in the treatment of seborrheic dermatitis with the aminoquinoline antimalarials. The mechanism of action is unknown, but Aralen (250 mg at bedtime) or Camoquin (200 mg at bedtime) has proved to be helpful in treating certain refractory cases.

Topical Therapy

Topical treatment is largely determined by the appearance and location of the lesions. Seborrheic dermatitis is basically an eczematous eruption which must be treated with mild compresses when it is acute and exudative as in the flexural areas. In the more chronic forms sulfur and salicylic acid are the tried and true topical remedies. These may be incorporated in 1 to 2% strength

lotion, in a paste or ointment, depending on the tolerance of a specific area or patient. Topical hydrocortisone preparations, which exist in literally dozens of kinds, have supplanted the classic sulfur and salicylic acid preparations for the treatment of small areas of involvement. Only trace amounts are needed for some dramatic results at times. For the seborrheic psoriasis lesions crude coal tar is used.

Scalp. Selsun Suspension is a recent and possibly the most popular treatment of dandruff [43-52]. It is a 2½% shampoo suspension of selenium sulfide which gives significant relief from the itching and scaling of mild seborrheic dermatitis of the scalp. For the usual case application is recommended once or twice weekly or less often as indicated—as follows

1. Wet head thoroughly with warm water wash with a bland soap and water and rinse (Some detergent shampoos are incompatible with Selsun. If a detergent shampoo is used it must be washed out of the hair very thoroughly before applying Selsun—unless it is definitely known to be compatible.)

2. Shake Selsun well. Pour an amount equal to 1 or 2 teaspoonfuls into the palm of the hand and work into scalp with the addition of a small quantity of warm water until a lather is obtained. Avoid contact with eyes

3. Rinse and repeat process. Allow Selsun to remain in contact with the scalp for a total time of at least 5 minutes.

4. Rinse scalp by using three or four changes of water or by showering with running water After treatment with Selsun, wash hands and under fingernails thoroughly

Numerous studies have testified to the effectiveness of this measure It is important to note that Selsun is of no value in the treatment of oily hair As many as 10 per cent of the individuals using Selsun will actually find an increase in the amount of scalp oil. The mechanism for this increase is unknown. Selsun is of no value in treating psoriasiform scaling of the scalp. The toxicity of selenium is well known, and the shampoo must be kept away from children. There is no evidence that appreciable or toxic amounts of selenium are absorbed when Selsun is used. I have observed several women in whom reversible thinning of the hair

developed coincident with the use of Selsun. Others have observed the same, and accordingly I avoid prescribing Selsun for individuals with a history of thinning hair In one patient, I have seen the development of a contact dermatitis of the neck and scalp due to Selsun.

Pragmatar is another proprietary highly effective in treating seborrheic dermatitis. It contains sulfur salicylic acid, and crude coal tar Small amounts are rubbed into the scalp every fifth night with a shampoo the following morning. Shampooing may be done with tincture of green soap or a tar shampoo such as Zetar shampoo [53, 54]

Sebizon lotion is another successful approach to the treatment of dandruff [55–59] It contains 10% sodium sulfacetamide which has antibacterial properties long used by the ophthalmologists. The lotion is applied to the entire scalp the night before shampooing. It is interesting to note that sulfanilamide lotion was once used as a dandruff treatment [60]

For nonproprietary prescription writing we use sulfur and salicylic acid in a water miscible base

Sulfur ppt.	3%
Salicylic acid	3%
Hydrophilic ointment U.S.P	

This can be applied to the scalp each night before shampooing. A standardized recent commercial version of this is Fostex cream, which can be used as a therapeutic shampoo in dandruff and oily scalp [61 62] Fostex cream contains the surface active cleansing and wetting agents lauryl sulfoacetate alkyl aryl polyether sulfonate, and dioctylsulfosuccinate with 2% sulfur 2% salicylic acid, and 1% hexachlorophene

Women generally prefer a lotion for the scalp We have found the following type successful in allaying the pruritus and scaling of seborrheic dermatitis of the scalp

Salicylic acid	2%
Resorcinol monoacetate	1%
Castor oil	5%
Spirit of lavender	5%
Ethyl alcohol	75%

This should be massaged into the scalp twice daily Be certain to use the monoacetate of resorcinol, since resorcinol itself causes a greenish discoloration of light hair Resorcinol preparations should never be used on infants because of the potential toxic or fatal effects from absorption.

None of these treatments are in any sense curative. Constant care of the scalp is necessary for as has been said [4] a French doctor discovered the only cure for dandruff—Dr Guillotin.

Eyelids. Seborrheic blepharitis usually responds well to any combination of antibiotic and topical steroid. We commonly use Neo-Cortef ointment 1%. It is inadvisable to use the tars, sulfur and salicylic acid in this area because of the possibility of conjunctival irritation and damage. Some observers have reported excellent results with a 30-minute treatment with Selsun cream (0.5% selenium sulfide in water miscible base) or with Selsunef ointment (0.5% suspension of selenium sulfide in a petrolatum base containing 0.5% hydrocortisone acetate) The preparations are removed by wiping with a clean cloth.

Ears. Again here any topical steroid with or without an antibiotic may produce rapid dramatic clearing. We commonly prescribe Neo-Cortef ointment.

In the retroauricular area fissuring is very often seen (Fig. 10-5) This complication can be effectively treated by the occasional application of Castellani's paint:

Basic fuchsin (sat. alc. sol.)	10
Phenol (5% aq sol.)	100
Filter at 2-hour intervals	
Boric acid	1
Acetone	5
Resorcin	10

Do not use if purple in color indicating deterioration which often occurs in a month or two.

Acute exudative retroauricular eruptions are treated with soft white cloth compresses, e.g., 30-minute application of room temperature Burow's solution (1 Domeboro effervescent tablet to a pint of tap water)

Face The same hydrocortisone, sulfur salicylic acid prepara

tions are effective. We commonly employ 1% Cort Dome Creme, Pragmatar or Acnomel Cake (a sulfur resorcin cake make-up base) One of these preparations may be applied sparingly once *a day to the affected areas only*

Trunk. The more extensive nature of seborrheic lesions on the trunk makes topical steroid therapy a less practical method of



Fig. 10-5 Typical secondary fissure in retroauricular seborrheic dermatitis. Castellani paint, applied once a day is very helpful in treating this.

therapy here because of the matter of expense. Sulfur and salicylic acid preparations are highly effective. Pragmatar has remained one of our favorites. Other prescriptions which are valuable include

1% Vioform (iodohydroxyquinoline) in a lotion or past
40% Sulfur in petrolatum
3% Ichthammol in zinc oxide ointment
10% Ammoniated mercury ointment
Chloromycetin ointment
Achromycin ointment
Sebizon lotion

Intertriginous Areas. In the acute exudative episode bed rest must be combined with 15 minute compresses three or four times daily (Domeboro effervescent tablets 1 to 1 qt of tap water) As the exudative phase subsides, Castellani's paint may be applied locally once daily with great benefit.

Topically steroids are valuable. We have found Neo-Cortef lotion 1% or Florinef lotion of considerable help. In many instances a 1 to 5% sulfur shake lotion proves, however to be the best-tolerated local medicament.

Dusting powders are also an aid.

APPENDIX Alternate Topical Considerations

There are literally hundreds of highly touted prescriptions and proprietaries which are useful in treating seborrheic dermatitis. The following are some of varying degrees of usefulness

Vitamin Creams

These may contain pyridoxine and other members of the B complex [22]

Quaternary Ammonium Compounds

These cationic surface acti e agents (methyl Benzethonium chloride Diaparene Bactine Hyamine) are used in a ariety of proprietaries (Cradol, Dandricide) [64, 65]

Sulfur Salicylic Acid, Tars Resorcinol

Appliderm resorcinol-sulfur ointment
Appliderm sulfur-salicylic acid ointment
Appliderm tar ointment
Ar Ex face powder w/sulfur
Ar Ex R M S lotion
Callo-Sul cream
Daxalan ointment
Dermasulf
Diasporal cream
Fostex cake—therapeutic skin cleanser
Intraderm sulfur solution
Neo-Supertah-5
Resorcitate
Resulin
Sal-Su Tar
Su A-Sa creme
Sulfur ointment
Supertah
Supertah ointment
Supertah c/sulfur and salicylic acid
Tarbonis
Tarcortin
Tarquinor cream
Tarquinor ointment
Ultar
Va Tar A
Va Tar B [a, 67 68]

Miscellaneous

Sebb (Vancide 89—antibacterial)
Teles (2.5% sulfated tellurium dioxide)
Viderma (bactericidal agent from plant) [69, 70]

One achieves the best results by using a few compounds skillfully and accordingly confidently Intelligent prescribing does not demand a mammoth repertoire. It is important to recall principles rather than new formulas.

Unanimous acclaim has long been given to the morbidistatic effects of sulfur salicylic acid, and the tars in seborrheic dermatitis. Modern clinical research has disclosed an additional group of three proved effective agents steroids, antibiotics, and selenium. These six groups are remarkably effective in treating all forms of seborrheic dermatitis.

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Harold Price

11

PSORIASIS

PSORIASIS IS A CHRONIC, recurrent disease of the skin of unknown cause, for which there is no specific therapy Response to treatment is often discouragingly slow and some eruptions appear to be refractory to all measures. Recurrence after a remission is common.

Keeping these facts in mind, one can perhaps understand how a physician may on occasion be provoked into uttering such cruel remarks to a patient as "There is no cure for psoriasis; you'll have to learn to live with it, or "Nothing can be done- you will have it all your life. One can understand, but certainly not condone, such a destructive and defeatist attitude. While psoriasis, admittedly presents a formidable therapeutic problem, it must by no means be considered a hopeless one. For the great majority of patients with psoriasis there are measures available which, under skillful management, can produce gratifying results.

Of prime importance is the general approach of the physician to the problem. His attitude must be one of reassurance and tempered optimism. The nature of the disease, the demands and difficulties of treatment, should be explained at the first visit. Perma

nent cure should not be held out, but adequate control, symptomatic relief and variable periods of remission should be the goals. It might even be mentioned that when an attack of psoriasis is cleared up with diligent treatment, the lesions may remain healed for long periods, perhaps for life.

The physician must ever keep in mind that he is not merely treating psoriatic lesions he is treating a human being who has a distressing cutaneous disease. In this sense he must assess the patient as a whole, determining how each individual feels about, and reacts to, the disease and to what extent emotional and tension factors are involved. In patients with few or minimal lesions who show no particular concern, it may be advisable to undertake no treatment whatsoever Other patients with similar lesions may be considerably disturbed and troubled and will require treatment. In any event, the patient must be made to realize that treatment will require active participation on his part, and the utmost perseverance and cooperation.

Psoriasis is usually considered a benign disease with no consistent causal relationship with other systemic diseases or abnormalities—a disease of healthy people, it is said. One exception is psoriatic arthritis, or as some prefer arthritis with psoriasis. But to persons with extensive psoriasis of the scalp or with ugly blotches on the face genitocrural involvement, or widespread distribution, the disease becomes a most distressing, unsightly and at times incapacitating one which may well interfere with a normal life. To the few unfortunates who develop the unhappy complication of exfoliative dermatitis, the misery the invalidism, the heavy economic burden of medical care, and the fatal outcome of some make psoriasis a dread and malignant disease

Persons with psoriasis throughout the world are hopefully awaiting the welcome news that a cure has been discovered. Regretfully it must be stated that although many new treatments have been advanced in recent years, on the whole no startling or significant contributions have been made. For the most part we have to rely on old remedies that have survived the winnowing passage of time and on newly reported measures which show

promise Inasmuch as various treatments seem to lose effectiveness after a time or are unsuccessful with other patients, it would appear advisable to accumulate a large store of effective alternate measures. To this end any form of therapy which has demonstrated fairly consistent beneficial results, and which presents little or no hazard, should be placed in what may be called a therapy reserve fund, to be drawn upon when needed

When we contemplate today the bizarre and somewhat frightening treatments of the past (intravenous injection of sulfur manganese, sodium salicylate, irradiation of the thymus and spine, insulin, gold therapy tobacco juice soaks) the sobering thought comes to mind that perhaps at some time in the future the accepted therapeutic measures of today will be regarded in a somewhat similar manner With this well in mind, I now proceed to a discussion of current trends in therapy of psoriasis

EXTERNAL TREATMENT

Topical applications are necessary for practically all cases. The selection of the proper remedy the concentration, and the vehicle will in large measure be determined by the site of the eruption and its morphologic characteristics. Treatment must be individualized and patterned to the stage and state of the lesions. Psoriasis which is acute, inflammatory and shows a tendency to spread or disseminate must be treated gently and kindly Substances having any irritating properties must not be applied at this stage. When the inflammatory aspects have subsided, antipsoriatic remedies can then be carefully employed. For the chronic, thickened, torpid patches, stronger agents are required and are usually well tolerated.

Patients object to messy staining, and odorous applications and will not long persist in their use. An attempt should therefore be made to prescribe the least objectionable and unpleasant preparations.

Crude Coal Tar Of the antipsoriatic remedies of merit, crude coal tar stands out as one of the best Applied as a 2 to 5% ointment or paste it yields fairly satisfactory results with persevering efforts B t crude coal tar ointments present the objections of

unpleasant color and odor and the incidence of irritation is high, in some tests over 13 per cent [1] Various attempts have been made to correct these unwanted features. Pflag and Zopf [2] discovered that the addition of small amounts of certain surfactants to coal tar ointment would reduce the size of the individual tar particle from as large as 100μ to an average of about 3μ, and that a more homogeneous dispersion of the tar was thereby effected. Carney and Zopf [1] prepared an ointment containing only 1% crude coal tar in which the tar was finely divided and uniformly dispersed by the addition of 5% of polyoxyethelene sorbitan monolaurate (Tween 20) The 1% ointment proved to be clinically as effective as the standard 2 to 5 % preparations. It was, moreover lighter in color had less odor and its irritant properties were markedly reduced. There are a number of other improved tar ointments on the market with similar advantages.† The new formula for coal tar ointment, U.S.P XV employs a nonionic surface-active agent. The tar concentration has been reduced from 5 to 3% A cleaner and more acceptable preparation is

Coal tar solution U.S.P (Liquor carbonis detergens)	10–20%
Hydrophilic ointment U.S.P	q.s.

In place of the ointment, patients may prefer to use full-strength coal tar solutions, U.S.P This is applied directly to the lesions once or twice daily with a cotton-tipped applicator

The method originally recommended by Goeckerman and O'Leary [3] utilizing crude coal tar ointment and ultraviolet irradiation has proved very effective for extensive eruptions. This procedure which is very messy and must be carefully supervised, usually requires hospitalization. A modification designed for the ambulatory patient consists of the following

1. A soap shower in the morning followed by application of coal tar solution, U.S.P

2. Before retiring, a soap bath followed by exposure to ultra

Available under trade name of Dispertar

† Tarquinor Zetar

violet irradiation from a General Electric R.S bulb. Dosage is adjusted to effect only a faint erythema.

3. Application of coal tar solution ointment follows the irradiation.

A valuable adjunct to this regimen is afforded by the gradual *tanning of the skin by sun-bathing. In fact, tanning of the skin* is an effective prophylactic measure to prevent recurrence. This is supported by the common observation that recurrent lesions frequently appear first on the untanned areas.

When lesions are covered with a thick hyperkeratotic layer 3% salicylic acid added to the tar ointment will aid in softening and removing scale.

Tar therapy may be accompanied by certain complications to which one must be alert: (1) Crude coal tar is a primary irritant and a sensitizer Evidence of irritation demands immediate cessation of tar application. If the contact dermatitis is a primary irritant effect, a reduction in frequency of application or a change to a milder preparation may be tolerated. (2) Certain fractions of crude coal tar are photosensitizers. Thus, when ultraviolet irradiation is combined with tar therapy the exposure dosage must be carefully controlled to prevent severe burn reactions. Patients who sun-bathe must be particularly cautioned that exposure should be brief at first and only slowly and gradually increased. (3) Tar has a tendency to cause folliculitis, which complication requires that treatment be discontinued temporarily

Special Sites. Because of special anatomical and physiological differences, certain intertriginous locations like the axillae, the genitocrural areas, and the gluteal cleft are prone to develop itching, eczematization, and secondary infection. Under such circumstances, Vioform cream 3% with 1% hydrocortisone serves admirably for symptomatic relief and to reduce the inflammatory and infectious elements. Although the local use of hydrocortisone preparations is of no value in ordinary psoriasis, inflammatory and pruritic lesions will often respond dramatically

Involvement of the ears often presents a troublesome problem with complications of secondary infection and lichenification. The following prescription is of value

Hydrocortisone	1%
Coal tar solution U.S.P	5%
Vioform cream	3% q.s.

In the management of psoriasis of the scalp, there exists the special problem of selecting remedies and vehicles which are not objectionable and which can easily be removed. Frequent shampoos are in order to aid in softening and removing scale and medicaments. An ointment which is effective and acceptable, since it is not messy and is readily washed out, consists of

Acid salicylic	2–3%
Ammoniated mercury	5–10%
Coal tar solution U.S.P	5–10%
Hydrophilic ointment U.S.P	*q.s.*

Recently a few reports [4, 5] have appeared which indicate that a preparation marketed under the trade name of P & S. Liquid, containing liquid petrolatum, sodium chloride solution, and less than 1% phenol, has been found to be highly effective for psoriasis of the scalp. Why this particular combination should be of value has not been determined.

Psoriasis of the nails can be most recalcitrant. Some cases do respond to x-ray therapy. There is also some evidence [6–8] that daily feedings of gelatin for periods of months will induce improvement.

Anthralin. For many years, strong substances like chrysarobin and anthralin have been used successfully, particularly for treating thickened, inveterate plaques of psoriasis. Certain disadvantages limit the usefulness of this form of therapy. Chrysarobin, and to a lesser extent anthralin, stain the skin, hair, nails and linen. Being primary irritants, they are apt to cause dermatitis and, on contact with the eyes, severe conjunctivitis.

In recent years, anthralin, a more stable chemical, has largely displaced chrysarobin. Treatment with anthralin requires the utmost cooperation on the part of the patient and close medical supervision. It should not be used for acute or spreading psoriasis. Starting with a 0.1% concentration, the ointment is rubbed in thoroughly into a few patches twice daily. The excess ointment

is removed and the areas are dusted with talc. Care must be taken to avoid contact with the surrounding skin, which often becomes stained and irritated. Evidence of irritation requires interruption of treatment for a few days. Gradually more areas are treated, and the concentration is increased slowly up to 0.5% The treatment appears to be better tolerated if the anthralin is incorporated in a zinc paste base instead of the usual petrolatum.

X-RAY THERAPY

Despite the current bad press and attitudes of fear and apprehension regarding ionizing radiation, it must be pointed out that for many years x-ray therapy has been used by dermatologists, and when intelligently and correctly employed with proper regard for dosage, the evidence of damaging effects is meager X-rays should be considered as another modality in the treatment of psoriasis, with special indications for its use. For instance, no other measure is of greater value, or will induce a more rapid response in psoriasis of the face, the axillae, cubital, and popliteal areas. Small fractional doses of the order of 75 r once weekly for 4 weeks will usually suffice to improve or clear up the eruption temporarily X-ray therapy should not be used routinely or promiscuously but should be reserved for particularly troublesome eruptions which have not responded to other measures. Of course, the necessary precautions to avoid irradiation of the gonads of procreative individuals must be observed.

Low voltage and grenz ray therapy which afford much less penetration through the skin and thus permit larger doses and repeated treatments, is almost as effective as conventional superficial x-ray therapy except perhaps in heavily scaling plaques. According to Klem [9] as much as 9,400 r have been administered in fractional doses over 13 years for the treatment of recurrent psoriatic lesions without evidence of unwanted sequelae

However it must be remembered that we are still dealing with ionizing radiation which can produce destructive changes in the skin, and the dosage schedule factors must still be carefully controlled to prevent excessive exposure

SYSTEMIC TREATMENT

The ideal treatment for psoriasis would be one based securely on knowledge of causative factors concerned. There are no indications as yet that we are even searching along paths which may lead to this goal. For many years, various and sundry reports have appeared extolling this or that form of systemic treatment for psoriasis, but none has been proved to be of consistent effectiveness. Arsenic, formerly considered almost a specific in psoriasis, has fallen into disrepute by virtue of its uncertain benefits, its toxic effects on the kidneys and liver and the tendency for the late development of keratoses, which may eventuate in squamous cell carcinoma.

Corticosteroid therapy is of no value in ordinary psoriasis. In psoriatic exfoliative dermatitis, massive doses will usually induce a prompt and dramatic improvement and at times is lifesaving. But the decision to initiate steroid therapy must be given thoughtful deliberation with due consideration and full regard for the complications and difficulties ahead. With large initial doses at levels of 60 to 80 mg of prednisone daily the erythroderma and exfoliation readily subside. As the daily dose is gradually reduced, one may find that the maintenance dose often requires fairly high levels—perhaps 30 to 40 mg. If steroid treatment is to be continued, serious complications can be expected. It has been said that once a patient with psoriatic exfoliative dermatitis is placed on steroid therapy it becomes almost impossible to get him off the medication. The physician soon realizes that he has a tiger by the tail and wishes earnestly that he had never grabbed hold. As far as corticosteroid therapy for psoriatic exfoliative dermatitis is concerned, it is my feeling that in the long run, the patient will be best served if steroid therapy is withheld, the only indication being its use as a lifesaving measure.

Triamcinolone (Aristocort, Kenacort) a new corticosteroid, is presently being evaluated in the treatment of psoriasis, and preliminary observations indicate that significant involution of lesions can be effected with relatively low doses. Sixteen to twenty milli

grams daily of triamcinolone will usually induce considerable involution to complete clearing in a short period of time. A maintenance level of 8 to 12 mg daily may then be required to prevent recurrence. Although it is claimed that side effects from triamcinolone present less of a hazard than that from other steroids, some serious complications have already been encountered. For the treatment of psoriatic exfoliative dermatitis, triamcinolone appears to offer definite advantages. However, inasmuch as the status of side effects has not, as yet, been adequately evaluated, the decision to subject a patient with a benign disease to treatment which may present hazards must be carefully considered.

Although the following case report does not warrant any definite conclusion, it is presented as a possible method of reducing steroid dosage:

> A patient with severe psoriatic exfoliative dermatitis had been placed on steroid therapy. Maintenance doses of 40 to 50 mg of prednisone were required to keep her comfortable. A number of attempts to reduce the dose resulted in acute flare-ups with associated lowering of serum proteins and edema. In this case a reduction of 10 to 15 mg maintenance dose has been accomplished by the use of Nilevar.

Nilevar is a new synthetic steroid, chemically similar to testosterone. It possesses strong anabolic properties but exerts little androgenic effect. In exfoliative dermatitis, large amounts of protein are lost in the scale. This in turn becomes reflected in lowered serum protein levels and a negative nitrogen balance. Nilevar may be of value in such conditions by aiding nitrogen retention and by correcting protein imbalance.

Pustular psoriasis of the palms and soles is an extremely chronic and treatment-resistant variety. Cormia and Noun [10] observed clearing of an extensive psoriasis with pustular psoriasis of the palms and soles when an associated lupus erythematosus was treated with quinacrine (Atabrine). Subsequently two other patients with pustular psoriasis, treated with quinacrine, also responded with prompt clearing of the eruption. Enthusiasm for this treatment was considerably dampened later when a few re-

ports [11 12] appeared relating that quinacrine and other antimalarial drugs could induce acute flare-ups and exfoliative dermatitis in patients with psoriasis.

For a number of years the idea has been advanced that psoriasis is related causally to disturbed pancreatic exocrine function, and that favorable clinical results can be obtained by pancreatic enzyme replacement therapy Entozyme and Lipan, commercial preparations containing pancreatin have been reported as having induced clinical remission in a high percentage of patients with psoriasis In a well-planned and controlled study Farber et al. [13, 14] have at long last laid to rest the claims for this kind of therapy *Their studies revealed that*

1 There was no evidence that pancreatic exocrine function was abnormal in psoriasis.

2. The administration of pancreatic enzymes did not in any way *influence the course of psoriasis. In fact, it was reported that* placebo therapy did slightly better than pancreatin.

A similar fate befell the claims that heparin was efficacious in psoriasis, when LeVan [15] conducted controlled studies. It is *interesting to note that his first six patients treated with intra* venous heparin responded quite well, but, significantly enough, six other patients given intravenous saline responded equally well. It would appear that suggestion or placebo therapy played an *important role.*

Practically every vitamin has had its turn in the treatment of psoriasis Recently the spotlight has been focused on riboflavin and vitamin B_{12} A concentrated solution of phosphorylated riboflavin *given intramuscularly was employed* by Luscombe [16] successfully in 44 patients. Ruedemann [17] reported enthusiastically that treatment with high doses of vitamin B_{12} (1000 micrograms) intramuscularly has surpassed all previous methods in rapidity of results. In the April 6 1957 issue of *Lancet*, Suzanne Alexander stated in Letters to the Editor that she had used vitamin B_{12} plus tar ointment and tar ointment alone in a control group *and found no particular difference in response.* Thus the true status of a new remedy remains obscure unless it is subjected to control studies

Aminopterin. A most interesting contribution to the systemic treatment of psoriasis which may point the way to a new and promising approach has been the use of aminopterin. This is a highly toxic drug, a folic acid antagonist, which interferes with the proliferation of epithelial cells. The treatment was first reported by Gubner [18] who found that responses were uniformly favorable with fairly high doses. However toxic effects were frequent, usually interfering with continuation of treatment. Rees et al. [19] demonstrated that with smaller dosage schedules, significant clearing could be achieved with little or no toxic reactions. They stated, "When aminopterin is used in a dose of 0.5 mg daily by mouth, not exceeding 6 mg in a period of 12 to 20 days, clearing or great improvement of psoriatic lesions occurred in approximately 80% of the cases with an incidence of toxicity of 8% Toxic effects on such a schedule were slight to transitory However recurrence rates were high, thus requiring retreatment courses This poses the problem of cumulative or delayed toxic effects. The possibility of prolonged or irreversible bone marrow aplasia is the chief concern Other toxic manifestations, as buccal and cutaneous ulcerations, temporary alopecia, and depression of blood count, promptly subside on discontinuance of the drug. The treatment may be indicated for severe *generalized psoriasis or exfoliative dermatitis. However* the general use of such a potentially dangerous drug is not warranted.

Chemical analogs of aminopterin have been prepared which are said to be less toxic and thus may be tolerated when administered continuously or in repeated courses. Further studies in this direction are indicated.

PSYCHOTHERAPY

There exist wide differences of opinion in regard to the effects of psychic influences on psoriasis. Attitudes range from the belief that emotional and tension factors are the essential cause of psoriasis, to the denial that there is any relationship. I think most dermatologists today take the middle ground that psychic factors are definitely operative in some but not all patients and that recurrence exacerbation, and remission are in large measure tied

to the psychological state. With some patients, given prior knowledge of stressful emotional or social situations, one may regularly predict an impending flare-up or recurrence.

There is experimental evidence that the skin of a person with psoriasis reacts to certain emotional stimuli with a characteristic vascular response. Graham [20] concluded from his studies that when patients were discussing those aspects of their lives which appeared to be relevant to their psoriasis, dilatation of arterioles together with increased tone of minute vessels was demonstrable. Milberg [21] observed that the reactive hyperemia threshold of individuals with psoriasis is higher than normal when the disease is active and decreases as improvement occurs.

Recently the new ataractic drugs have been reported to be of value in treating psoriasis. Certainly this is not a specific effect, and whatever benefits may be derived are very likely from the ataractic action. Phenobarbitol, a much less expensive medication, probably does as well.

Along with sedation, support and reassurance are necessary adjuncts. An attempt should be made to identify major emotional and stress factors. The need for physical and mental rest, relief of tension and escape from stressful situations should be emphasized. It is sometimes remarkable how quickly psoriasis will respond to lolling in the sun on a few weeks' vacation, away from it all. During a sharp upswing of psoriasis, this therapeutic measure may be imperative.

Obermayer [22] doubts the validity of claims of cure by psychiatric management. However he feels that psychotherapy is a necessary adjunct in the management of the patient with severe generalized psoriasis. Patients who manifest severe emotional disturbances should of course be referred for psychiatric care. In the event that psychoanalysis is attempted, it would be wise to have concomitant dermatologic observation. The analyst should be kept informed of the status of the psoriasis, for there is the danger of precipitating an exfoliative dermatitis through intensive psychoanalysis.

In conclusion, it may be stated that the present treatment of psoriasis is far from satisfactory and it is likely to remain so until

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Edward L. Laden | **12**

ACNE VULGARIS

THE CLINICAL TRIAD of acne vulgaris is seborrhea, comedo formation, and an inflammatory reaction which may appear as an erythematous papule, pustule, nodule, or cystic undermining lesion.

CAUSATIVE FACTORS

Before entering into a discussion of the therapy of this disease, it would seem appropriate to comment briefly on those factors which are of importance in the production of the various parts of this triad

Endocrine. The increase of sebaceous gland excretion with oncoming puberty is apparently related to endocrine influence. It is associated with an actual increase in sebaceous gland volume, which reaches its maximum some time after puberty after which no further growth of the gland takes place. In the male, the testicular hormone is recognized as the principal one causing this change Thu it is known that in castrated or eunuchoid males, acne and seborrhea do not develop, but if these same individuals are treated with testosterone such changes can be produced. In the female present research indicates that proges

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rhea is commonly observed. It is possible that this change is indirectly produced by hormonal stimulation via nerve tracts leading to the pituitary The same may be true in emotion created seborrhea.

Comedo Formation. The development of the comedo is an even more significant change in acne than is seborrhea, since the comedo is the primary lesion of this disease. Despite this, very little is known about the actual mechanism of its production. The original concept of Unna and others to follow was that the comedo is a reaction of the horny cells to the presence of the acne bacillus multiplying in the infundibulum of the pilosebaceous follicle As Unna first showed, the comedo results from hyperkeratosis at the mouth and upper part of the follicle causing a retention behind it of the sebaceous matter Unna also proved that its dark color is due to the oxidation of keratin. At the present time however it is believed that comedo formation is the result of stimulation of keratinization exerted by androgen in the male and possibly progesterone in the female. The manner in which these hormones create this change is not understood. There is evidence that estrogen and androgen are each important in the life processes of epithelial tissues, including the skin. Estrogenic stimulation on epithelial proliferation, cornification, and desquamation in rhesus monkeys and guinea pigs has been studied. ACTH and cortisone also appear to play a part in the production of follicular hyperkeratosis, again by mechanisms which have as yet not been worked out.

Vitamin A. The role of vitamin A in keratinization has been of interest. It is known that the presence of vitamin A is essential for normal epithelial cell development and in vitamin A deficiency states, abnormalities of keratinazation may be observed. The best known example was the observance of follicular hyperkeratosis in itamin A deficient Chinese by Frazier and Hu in 1931 This condition was cured by the administration of vitamin A. Since that time itamin A has been used in the treatment of various diseases, including acne in which abnormalities of keratinization occur and particularly for follicular hyperkeratotic disease. However there is no proof at this time that the keratini-

zation anomaly of follicular orifices in acne vulgaris is influenced beneficially by vitamin A.

Ultraviolet Light. The effect of ultraviolet radiation on keratinization has been appreciated for many years. Its action on ichthyosis, for example, is to produce a nonspecific normalizing effect on the abnormal keratinization. In acne, there is evidence that it also normalizes the keratinization process.

Inflammation. The inflammatory reaction in the final phase of acne is of great interest. The theory that it is produced by bacteria growing in the plugged-up pilosebaceous follicle and that the acne lesion is therefore the result of infection is not supported by the known facts. The organisms found in the acne lesion are principally *Corynebacterium acnes* (so-called acne bacillus) *Staphylococcus albus* and the hemolytic *Staphylococcus aureus*. Of these the last is the only one now recognized as a pathogenic organism It is the organism so commonly found in the various cutaneous pyodermas. Although it is notorious for its ability to develop resistance to the various antibiotics, it is among the most susceptible of organisms when first exposed to the various antibiotics. Even the most enthusiastic advocates of antibiotic therapy for acne could hardly claim that the response of acne to antibiotic treatment resembles that of the typical pyoderma.

The histological changes of the acne lesions are not those of a pyoderma. The presence of giant cells and the granulomatous type of infiltrate is not characteristic for a pyogenic lesion In many respects the inflammatory reaction of acne is like a foreign body reaction. Histologically there is much resemblance to such a change Clinically it is commonly observed that the opening of the lesion and extrusion of the sebocomedo body usually found in such a lesion is followed frequently by rapid healing.

An unanswered question is What accounts for the difference in severity of inflammation between individuals? Hormonal differences of any significance have never been demonstrated as the cause. The causative factors of diet emotional disturbances, and mode of life all have their adherents. The role of allergy in this reaction has received little attention, and yet there is clinical evidence to suggest that the more severe reactions may represent

a hypersensitive reaction on the part of a hyperreactive individual. This may represent a constitutional difference, which in turn may be inherited. The fact that ACTH and cortisone are effective in suppressing these severe inflammatory reactions of acne has now been reported. The conflicting position of these hormones, first being able to produce an acneiform eruption in hypersteroid states but also modifying the reaction of the acne lesion, is of interest. Further studies must be carried out to establish whether so-called allergic individuals are more prone to severe acne; also whether excessive reaction to the keratin or inspissated sebum can be demonstrated in such persons as compared to the normal.

Summary. In essence, then, acne vulgaris is a disease characterized by the development of a keratin plug at the mouth of the pilosebaceous follicle. The reaction to this comedo and the dammed up sebum may be long delayed, but eventually in a high percentage of such dammed up follicles, an inflammatory reaction develops, resulting in a papule and eventually a pustule. If the reaction is mild to moderate, the pustule opens, and the comedo and retained sebum are discharged, resulting in healing of the lesion. In a certain number of cases, the reaction is more intense and involves the deeper portion of the skin, resulting in an indurated nodule. The most severe reaction is the breakdown of the nodule to form a cystic reaction which, not being able to discharge to the surface, may undermine and connect with other lesions. These deeper lesions, because they cause destruction of dermal tissue, result in scar formation.

TREATMENT

There are many ways to treat acne vulgaris. Each in its way attempts to counteract some or all of the triad of seborrhea, comedo formation, and inflammation. None of these measures is really curative; all are palliative, attempting to control acne and prevent scarring until the passage of time brings about a cessation of the process. Nevertheless, such palliation is eminently worthwhile, particularly since it can be relatively very effective. The psychic trauma resulting from neglected acne can be formidable. Scarring, which could have been prevented, may be quite

severe and, despite present techniques for improving such changes is to a considerable extent permanent. The attitude of not treating acne or waiting until nature takes its course is to be condemned. Acne can be well treated by the nondermatologist if he will merely take the trouble.

External

The effectiveness of topical medication is not always easy to evaluate. In relatively mild degrees of acne, such measures may be apparently very effective in more severe cases, the results are not as effective. In general, however the more persistent the individual is in carrying out such applications, the more benefit can be expected.

Special Soaps and Cleansing Agents. The rationale behind the use of such cleansing agents is to combat seborrhea and comedo formation. Soap and water removes the oily film but this is soon replaced by the flow of more sebum onto the surface. If the cleansing is carried out several times daily there will be relatively less oil on the surface than if the face is washed less frequently That this matters in control of acne is hard to understand. If the washing is carried out with vigor such as may be accomplished with use of a wash cloth or complexion brush and hard rubbing, eventually an irritation is produced and a dermatitis. Such a dermatitis may result in a dryness and scaling of the skin which actually improves the appearance of the acne although there always exists the problem that in a susceptible individual the irritation may proceed to a point where the dermatitis becomes more of a problem than the acne. Such strong soaps as sapo mollis or tincture of green soap are more likely to produce such irritation Soaps to which sulfur has been added are perhaps more irritating than regular soap Germicidal soaps such as Dial or Phisohex are reported to be effective in reducing the bacterial count of the skin, but they have not been proved to be more effective than ordinary soap in the treatment of acne In essence then, soap and water cleansing is desirable If it can be carried to the point of creating mild dryness and no further irritation it can improve acne. In some individuals stronger soaps such as sapo

mollis are useful in creating this dry state. As to the converse, creams and occlusive cosmetics should be eliminated. In addition to cleansing the skin involved with acne, frequent cleansing of the hair and scalp is desirable. For this purpose, Selsun and other shampoos are useful.

Topical Medications. Most of the commonly used preparations contain salicylic acid, resorcin, and sulfur singly or in combination. The first two agents are keratolytic and included for their ability to cause peeling, which may eliminate or prevent comedo formation. Sulfur is a so-called antiseborrheic agent which is believed to counteract seborrhea and normalize sebaceous gland function. It is also a skin irritant in proper concentration as well as an antibacterial agent. All these agents are primary irritants in sufficient concentrations, and one must adjust the concentration to the skin of the individual patient. One of the troubles with the prepared acne agents on the market is that the concentration of the medicines in them is fixed and does not take into account the sensitivity or resistance of the individual under treatment. Thus many individuals will not tolerate a concentration of 8% sulfur which is the amount present in certain of these agents.

Some of the agents in common use are Lotio Alba (White Lotion) N.F. consisting of zinc sulfate 4%, sulfurated potash 7% in distilled water; Acnomel, resorcin 2%, sulfur 8% in an oil in water base; Kummerfeld's Lotion (modified) sulfur 6%, tragacanth 1.5%, ethyl alcohol (95%) 10% and spirits of camphor 10% in water. Although these preparations and others are of value, it would seem wiser to individualize the concentration of the active ingredient. This can be done by utilizing the special, prepared tinted lotions for oily skin and adding to these the desired quantities of resorcin and sulfur. These concentrations can then be increased or decreased as the case warrants. A good plan is to start with concentration of 2% resorcin and 3% sulfur. This is usually well tolerated by even relatively sensitive skin. As this is used, the concentration of sulfur may be increased even to levels of 8 to 10%. Usually it is preferable to keep the resorcin concentration no higher than 3%.

Carbon dioxide slush is a special form of topical therapy which is of value. The simplest technique is to store the CO_2 in tanks. By using a small bore tube around which a chamois or chamois bag can be wrapped, the CO_2 condenses into solid dry ice. This is then wrapped in gauze and held with a hemostat. Another source of the CO_2 may be the so-called Kidde apparatus. The CO_2 is then dipped in acetone and quickly wiped across the involved skin. The result is a superficial freezing effect which can be regulated by the physician to cause mild redness up to a strong peeling.

Ultraviolet light is another special form of topical therapy. The cold quartz therapy unit can be used to produce redness and peeling. The hot quartz, which produces rays of the sunburn spectrum, has an effect akin to natural sunlight. This for many patients is of much benefit. It tends to normalize keratinization and reduce the development of comedos. It seems to have an antiseborrheic effect in addition, and many individuals find that, when they are able to obtain regular and prolonged sunlight exposure, their acne lessens considerably. Unfortunately, the hot quartz ultraviolet lamps reasonable enough in cost are not able to duplicate the complete effect of natural sunlight. Nevertheless, they are worthwhile, and such relatively inexpensive bulbs as the R.S. ultraviolet produced by General Electric and Westinghouse can be recommended for home use.

X-ray therapy is a form of local therapy which at the present time has become a controversial subject. For years it has been the most potent weapon available to the dermatologist in the treatment of acne. Although some have questioned how real its effectiveness is in the doses which might be considered safe, the fact is that the majority of dermatologists have and perhaps still do consider it their most reliable tool for bringing about an end to activity in this disease. Despite this, the fundamental question has been raised as to whether it is proper and wise to treat a disease of this nature with an agent which may in later years be responsible for possible neoplastic development as well as induce changes in subsequent offspring of a group who may soon be entering into the childbearing age. Since this fundamental ques-

tion cannot now be satisfactorily settled and since the burden of proof seems to have shifted to the side which is using x-ray therapy it is the author's opinion that x-ray therapy will gradually be abandoned in the treatment of this disease. Apparently some of the more influential teaching centers are no longer advocating x ray in the therapy of acne.

Surgery It is in this field that the generalist can perhaps do the most for his acne patients if he will care to take the trouble. Acne surgery means the removal of comedos with the comedo extractor the draining of pustular and cystic lesions. In addition there is the removal of large sebaceous cysts and for the special ist the use of dermal abrasion to improve scars. It should be emphasized that merely draining the developed lesions, removing comedos, and opening and removing milia will bring about obvious improvement if this procedure is repeated at regular intervals. It is true that this is palliation rather than cure, but it does clear the individual lesions and prevent new ones from forming. In addition, there is no reason why an interested member of the patient's family cannot be trained to do some of this work at home

Internal

Although acne is a disease of internal cause, the internal treatment of this disease leaves much to be desired. There can be little doubt that the future will provide such agents which act directly on the causes of acne, but at the present time such a therapeutic milestone has not been reached. There are, however certain internal measures which are in current vogue and which to some extent may have an influence on the course of the disease. Chief among these are the following

Antibiotic and Chemotherapeutic Agents. It is currently advocated by some that prolonged therapy with such agents as the broad-spectrum antibiotics or one of the sulfa agents carried on for periods of weeks and months will bring about definite improvement. Dosages recommended for this therapy such as 125 to 250 mg of tetracycline daily are well below those used in short term therapy of the usual infections. It is difficult to understand

how such therapy can influence the pustular phase of acne. If one is willing to accept that such pus development is due to secondary *invasion by bacteria*, and this has not been proved, then one must believe that the hemolytic *Staphylococcus aureus* is the responsible organism, at least, this is the principal pathogen cultured from such lesions. From what is known about this organism's ability to develop resistance to the antibiotics, it is difficult to believe that it could be controlled or eliminated by such small doses. In fact, one is disturbed by the realization that we are more likely developing organisms which will be quite resistant to the particular agent in use and perhaps capable of causing more serious disease. It is of course possible that these antibiotics do their work elsewhere such as on the flora of the gastrointestinal tract and indirectly influence the acne lesion. This has not yet been proved. On the basis of the above, it is recommended that antibiotic theory if used in acne, be restricted to short-term therapy and that doses used be those accepted in the therapy of the usual infection. It would perhaps be wise to precede such therapy by bacterial cultures and the determination of antibiotic resistance of the isolated organisms.

Estrogenic Hormones. The use of estrogens in therapy of acne seems a logical sequence of our present knowledge of the role of androgens in the cause of acne. Unfortunately such agents have never achieved a really proved place in the therapy of this disease. There are numerous articles advocating estrogen for treatment of acne in the female. The dosages recommended are in some instances quite high, and one is reluctant to administer them to an otherwise normal female. It is true that as a rule one does not see much ill effect other than the cessation of menses, but this author has never had the courage to continue such large doses for periods of any length. Doses of a more conservative nature such as Premarin 0.625 mg per day or diethylstilbestrol 0.25 mg per day have usually not created any very noticeable effect. For males estrogens are difficult to administer over a long time because of their ability to cause a possible testicular atrophy. Certainly they cannot be considered a practical method of treating acne in males.

Steroid Therapy The treatment of acne with drugs of the cortisone-ACTH group is one of the most recent developments and one which has occasional indications. These drugs seem to act by suppressing the inflammatory phase of the disease. Although they are not curative, and on their discontinuance inflammation may eventually return, they can provide a valuable short time tool for halting a very severe destructive type of acne process. Thus in a severe cystic acne, a short course of steroids combined with antibiotic therapy often brings about marked improvement. During this respite, other therapy such as acne surgery can be instituted to drain cystic and pustular lesions as well as remove comedos. This approach to the problem has at times been very gratifying and well tolerated by the patients. Obviously steroids as long-term therapy for acne cannot be recommended.

Diet. The belief that diet is a major factor in the production of acne is so widespread among the general population that treatment which does not emphasize this regime is bound to be met with surprise by the patient's family Nevertheless, there is no proof nor even good clinical support to the concept that either a low fat or low carbohydrate diet will benefit acne. Whether individual foods such as chocolate, nuts, cheese, peanut butter pork, and milk can cause exacerbation of acne lesions is also not proved No strictly controlled studies are known to the author which have proved the effect of these foods. In some cases it may be wise to suggest a trial and error approach to the problem. Elimination of these foods for a period of say 2 weeks and then their addition one by one to the diet, and watching for flares is one approach to the problem. Since in general such patients are in a rapidly growing phase of life, in which high caloric foods are considered desirable it seems unjustly severe to eliminate them without sound reason. The common practice of families to blame the poor patient for every deviation from a too strict diet and to find cause for every exacerbation in some fault of the individual creates only unjustified guilt and anxiety

Vitamins. Reports have appeared in recent years and continue to appear of the relative effectiveness of high doses of such vita

mins as A, B complex, and D in the treatment of acne. It is doubtful, however whether such observations have been generally confirmed by the majority of observers.

TREATMENT OF SCARS

Efforts to lessen the scarring which unfortunately is an all too common sequela of acne vulgaris have been made for many years. The method now in current vogue is the so-called dermal abrasion. The technique which requires special training, is being practiced by many dermatologists and some plastic surgeons. The results of this procedure are difficult to evaluate in an objective fashion In general, the patients show a high degree of acceptance of the results initially Their enthusiasm often outweighs that of the physician who has carried out the procedure Photographs of before and after are of aid but are not always reliable indicators. Nevertheless, it is generally accepted that improvement is produced in most of the patients so treated. It is a mistake, however to create the false impression that the majority of scars are actually eliminated.

The literature on the therapy of acne vulgaris is massive, and no effort has been made to summarize it. Obviously many different viewpoints exist regarding much of the material presented, but it is the author's opinion that a report which recounts the various, often opposing, attitudes without stating one's own conclusions is only confusing and of no practical value to the reader

In conclusion, therefore, a physician can with the use of acne surgery carbon dioxide slush application, and topical medication improve *a large majority of his acne patients. In addition,* the ultraviolet light, particularly for home use, can be of great aid. At times the judicious use of antibiotics and steroids for short periods may be indicated.

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single grossly evident lesion. The adjacent 99 glands may continue to function normally. An analogy with folliculitis may be in order once it is realized that the miliarial lesion does not reveal its appendageal site. The clinical changes are most striking and

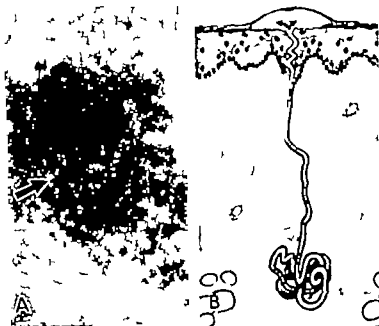


Fig. 13-1 *Miliaria crystallina.* A. Superficial asymptomatic vesicles characterize this harmless sweat retention entity. B. Histologic diagram shows that the sweat is trapped in the outer dead horny layer of skin. (D. M. Pillsbury, W. B. Shelley, and A. M. Kligman, *Dermatology.* Philadelphia, W. B. Saunders Company, 1956.)

distinctive in the primary miliarias. Here, it is possible to distinguish three major types: crystallina, rubra, and profunda (Figs. 13-1, 13-2, 13-3). In each case the level at which the sweat extravasates is the determinant of the clinical appearance. In miliaria crystallina the sweat breaks through the duct into the most superficial layer of the epidermis—the stratum corneum. Here the trapped sweat remains as a transparent dew drop. This condition is noninflammatory, asymptomatic, and insignificant

[5] It can be recognized and erased by a single stroke of a towel. In miliaria rubra, the classic prickly heat, the sweat escapes into the epidermis producing vesiculation, pruritus, burning, and erythema [6] In miliaria profunda the sweat escapes into the corium and as such produces only a noninflammatory papule,

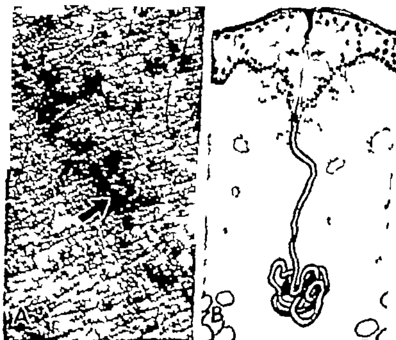


Fig 13-2. Miliaria rubra (prickly heat). A. Small pruritic erythematous papulovesicles characterize this common summer affliction B Histologic diagram shows that here the symptoms and signs result from escape of the sweat into the midepidermis with considerable cell damage, and subsequent local inflammatory infiltrate as well as pruritus. (D. M. Pillsbury W B. Shelley and A M. Kligman, Dermatology Philadelphia, W B. Saunders Company 1956)

which waxes and wanes with sweat production Usually this is a late sequela of repeated attacks of miliaria rubra and results from deep epidermal plugging of the eccrine pore It has been seen in the tropics and is associated with severe heat intolerance purely because of the very high number of glands affected In

many instances nearly every sweat gland in the body is involved [8]

Attention must be directed here to a rare type of miliaria, or sweat retention, associated with poral closure of the apocrine

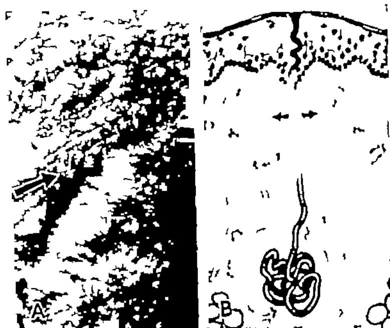


Fig. 13-3. Miliaria profunda. A. Flesh-colored, noninflammatory, asymptomatic papules are seen in this generalized eruption, which produces tropical asthenia. Each papule is the site of an occluded gland. The heat intolerance results from the large number of glands involved. The elliptical clear portion is the biopsy site where the affected glands were removed. B. Histologically one finds a deep keratinous plug with rupture of the subepidermal sweat duct. Edema of the corium is seen due to local escape of the sweat. (D. M. Pillsbury, W. B. Shelley and A. M. Kligman, Dermatology. Philadelphia, W. B. Saunders Company, 1956.)

sweat glands. We have labeled this apocrine miliaria [4] heretofore it was described as Fox Fordyce disease, or chronic pruritic eruption of the axillae. It is to be sharply distinguished from the common eccrine miliaria group by the following points

1 Usually seen in women (puberty to menopause)

2. Clinically noninflammatory follicular papules (Fig. 13-4)
3. Appears only in apocrine gland areas axillary mammary pubic, and vulvar
4. The apocrine but *not* the eccrine glands are occluded.

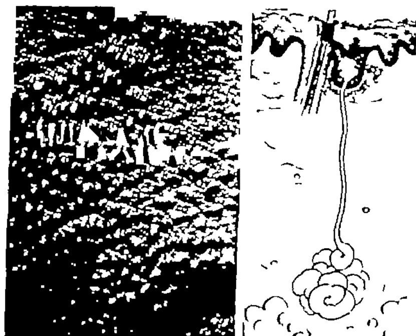


Fig. 13-4 Miliaria apocrine (axilla). A. Follicular pruritic papules found only in the apocrine areas are diagnostic of apocrine sweat retention entity. Adrenergic stimuli will induce pruritus because of escape of trapped apocrine sweat. B. Histologic sketch showing occlusion of the apocrine sweat pore and rupture of terminal duct. (D. M. Pillsbury W. B. Shelley and A. M. Kligman Dermatology Philadelphia, W. B. Saunders Company 1956.)

5. Waves of severe pruritus are associated with emotional tension.
6. The cause is hormonal not due to surface maceration.
7. Course is exquisitely chronic rarely showing involution.

Treatment of apocrine miliaria is not satisfactory No specific means are currently available either for inhibiting apocrine sweating or for removal of the follicular occlusion.

SECONDARY MILIARIA

Miliaria rubra remains the prototype of primary sweat retention. It, however may occur also as a secondary phenomenon in various dermatitides. Actually secondary miliaria appears in many guises and occult forms. It is not easily put into tidy diag

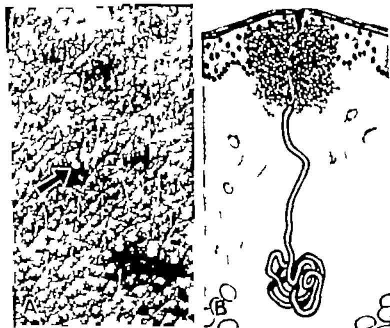


Fig. 13-5 Miliaria pustulosa. A. These pustules arise as result of eccrine sweat retention in dermatitic skin. Note that they are not follicular in location. B Histologic view of leukocytic infiltrate in sweat retention pustule (D. M. Pillsbury W. B. Shelley and A. M. Kligman, Dermatology Philadelphia, W. B. Saunders Company 1956)

nostic designates; yet one sees the vesicles and erythema of miliaria rubra and also lichenoid papules which may represent a form of miliaria profunda. Actually the most distinctive form of secondary miliaria is the pustular form, miliaria pustulosa (Fig. 13-5) [9] Here a pustule develops intraepidermally where the escape of sweat takes place. This pustular miliaria is often

mistakenly diagnosed as folliculitis candidiasis or bacterial infection.

The diagnosis of the secondary miliarial syndromes is often an *intuitive process which arises from an awareness of the correlation of sweating with exacerbation of a dermatitis.* However it is possible by infiltrating a test site with atropine sulfate (1/10,000 aqueous solution) to eliminate temporarily the miliarial element locally. Precise morphologic information can be had only by *securing a biopsy of representative suspect lesions,* having this serially sectioned, and locating the vesicle or pustule along the sweat duct. This formidable procedure is rarely done. Routine biopsy study is often unrewarding, since the pathognomic change is seen *only* at the sweat pore.

In my experience secondary sweat retention is seen in many eczematous processes [2, 10]. Miliaria commonly develops in the axillae of susceptible individuals following the use of antiperspirants, or simply in association with the maceration of hyperhidrosis. It may be wrongly identified as a contact dermatitis or seborrheic dermatitis *if one fails to recall* the rather constant emotional sweating some people experience in this particular area. Miliaria is probably the most significant secondary change to be seen in atopic dermatitis or infantile eczema. One should recall that the infant lives most of his time in the mother-made tropics *of his cradle. Here, miliaria, both primary as well as* secondary occurs at Christmastide as well as on July 4. The diaper dermatitis is another example in which miliaria develops and contributes to the chronicity of the primary process. In older patients seborrheic dermatitis and eczematous contact dermatitis may *show secondary miliaria.* Intertrigo very often presents secondary miliaria. Miliaria is a common cause of itching, and in a wide variety of normally nonpruritic dermatoses, secondary miliaria may account for an otherwise puzzling pruritus. Psoriasis is an example in which we have seen pruritus develop because of secondary sweat retention. Although miliaria may develop in atopic dermatitis, appearing as a fine papular eruption best seen in cross lighting, sweat retention also commonly manifests itself solely by pruritus or increased erythema. Here the clinician

must have an awareness of the problem before he will discern any examples.

Miliaria is not a bacterial infection of the sweat gland. Yet in infants severe local infections may develop in the occluded sweat gland. This receives the name of periporitis staphylogenes [11] Clinically it presents itself as multiple furunculoid lesions. Systemic antibiotics are indicated and are effective. At times culture and sensitivity typing of the causative organism are necessary

PATHOGENESIS

The cause of primary miliaria is the prolonged maceration of the skin surface by unevaporated sweat. Indeed it is possible to produce miliaria experimentally by simply keeping an area covered with wet compresses for several days [12] At the end of this time abnormal keratinization has occluded the terminal sweat pore. This occurs uniformly and manifests itself only negatively as asymptomatic anhidrosis. No sweat appears on the skin surface. In the presence of a continued stimulus to sweat, only susceptible individuals show the development of miliaria. Here, the intraluminal pressures within the gland lead to rupture of the duct at the weakest point below the occlusion. This is ordinarily in the intraepithelial portion so that sweat extravasates into the epidermis producing the clinical vesicles, papulovesicles, and papules. The lesion results directly from the sweating, so that a varying clinical pattern ensues, depending on the activity of the gland [13]

Recent studies have shown that the plug is initially not keratinous material, but rather a Schiff's reagent-positive, diastase-resistant material [14] Later there is degeneration of the epidermal sweat duct unit. Then a parakeratotic "keratin plug, formed by the old degenerated sweat duct, occludes the new regenerated epidermal sweat duct unit. In this way a self perpetuating process is established provided that sweating occurs at weekly intervals.

The significance of the individual susceptibility is considerable. Some people never develop miliaria despite repeated occlusion of the gland and prolonged stimulation of the gland. Others show repeated bouts of miliaria both of the primary and secondary

type [15] In these individuals the process of sweating in the presence of occluded pores results in miliaria no matter what the stimulus for sweating may be It is a significant fact that emotional stresses may well produce pruritic exacerbations of skin disease by the simple physiologic process of initiating sweat secretion in occluded glands [16]

Some observers have found that the surface microflora are intimately concerned with the pathogenesis of miliaria [17 18] They view the distal duct obstruction as a reaction to the surface staphylococci or *Candida albicans* We would prefer to view the miliaria as a result of local epidermal injury rather than consider the process as a classical pyoderma or candidiasis. Certainly a wide variety of nonspecific trauma to the epidermis will initiate miliaria in susceptible subjects.

TREATMENT

The treatment of miliaria in all of its forms, types, and locations is highly specific and satisfactory It consists in simply eliminating the cause sweating [19, 20, 21, 22] Once sweating stops, all the acute manifestations of miliaria disappear in several hours. The pruritus abates as soon as the sweat is no longer pumped into the epidermis In turn, one sees the erythema fade and papulovesicles collapse within a day or two All that remains is the postinflammatory scaling or the primary dermatitis. The poral plugs or caps remain for from 1 to 3 weeks but these are invisible usually to the naked eye. After this the pores spontaneously return to the normal patent state However should any degree of sweating occur during the normal desquamative process while poral occlusion still exists further epidermal damage is done with a prolongation and extension of the reparative time period [14] It is thus imperative to eliminate or at least greatly reduce all eccrine sweating during the healing phase to permit the most rapid recovery possible

Environmental Change Since the major stimulus to sweating is thermal, one must attack this. It is important to explain to the patient that persistent sweating means a persistent miliaria. Adequate steps must be taken to reduce the heat load on the

body The most radical approach had to be used in the tropics with troops suffering from generalized miliaria. The men were flown to a cool climate. Within 24 hours of reaching San Francisco some men experienced virtually a miraculous cure of generalized eruptions which defied accurate labeling, yet were predominately miliarial. In civilian practice the air conditioner has proved to be a boon to many patients in the southern areas. We strongly advise the purchase of a room air conditioner for patients with chronic dermatoses regularly aggravated by miliaria during every hot spell in Philadelphia. Many of these patients should find work in air conditioned buildings if they cannot spend their summers in the north woods.

Ventilation. Less dramatic but often adequate measures include efforts to increase ventilation. Fans may be employed. Certain parts of the house or employment area may be distinctly cooler One should attempt to find the less humid environment and also the shaded area, thereby promoting evaporation as well as reducing the radiant heat load. Once the patient realizes that all hinges on reduction in the need for sweating, he will cooperate. Reducing his work load, taking showers, wearing fewer clothes, each may be a critical injunction. Certainly the helpless infant must be freed of his maternally produced tropical environment.

Alleviating Emotional Stress. Emotional stresses may stimulate the sweat glands also, since the sweat glands are under autonomic control. These may account for the flashes or waves of generalized pruritis one may immediately experience during acute emotional tension. Many patients have been helped with the various tranquilizing drugs once the association of tension and pruritus has been adequately recognized. We have employed Equanil, Thorazine, and Serpasil with variable results. Recently we have used a phenothiazine derivative, Temaril (at present available only for investigative studies) with striking antipruritic properties in clinical practice. It has, however no direct effect on the sensation of pruritus as experimentally elicited. We are inclined to suspect that at least some of its clinical effectiveness may derive from a reduction in the autonomic outflow to the sweat glands.

Anticholinergic Drugs. The use of systemic anticholinergic drugs would seem to be the ideal logical way to control sweating and thereby miliaria. However practically one has the problem that heat collapse, pyrexia, and other serious complications will ensue in any patient in a hot environment in whom all sweating is appreciably curved. Sweating is a necessary defense against the threats of an excessive heat load. Should we remove this defense, the individual must retreat from the hot environment or suffer all the serious, at times fatal, effects of heat intolerance. Accordingly we have tended to eschew atropine, Banthine, and Prantal for systemic use.

Topical Therapy. Topically too little can be done from a positive standpoint. The major desideration of any topical therapy here is the elimination of the poral obstruction, but this remains unattainable from the practical standpoint. The focal keratinization defect extends deeply into the epidermis. It does not respond to such classic desquamating agents as salicylic acid (5% in alcohol) since these operate in the outer epidermal strata. Moreover the patient with miliaria has essentially delicate skin and these peeling lotions may well be a double-edged sword producing surface desquamation, as well as further epidermal injury and plugging of the pores. It has been our experience that the sweat pore is uniquely susceptible to the action of irritants.

In lieu of removing the poral plug, opening the pore functionally would be a highly effective therapeutic approach. Actually in miliaria profunda it has been shown that anhydrous lanolin inunction is followed by sweating in the exact area treated. The lanolin in some way relieves the poral occlusion so that sweat can reach the skin surface. Other than in the tropics where miliaria profunda is usually seen, lanolin has limited usefulness. In any event lanolin does not provide relief in cases of miliaria rubra or pustulosa.

Despite the general inefficacy of local measures, the patient will insist on this approach. If he is not given a topical prescription by the physician, he will almost invariably soon try a variety of sensitizing measures, hopefully proposed by neighbors who used them with success (just before that break in the last heat

wave) We generally prescribe an anesthetic type of lotion as Tronothane or Quotane for use as needed for the relief of pruritus. Phisohex, Dial, or Lifebuoy soap is prescribed for cleansing with a view to reducing the bacterial flora. Maceration leads invariably to enormously high surface bacterial counts. If superficial pyoderma exists, Chloromycetin cream is prescribed. A neomycin lotion has also been used with some success [23, 24] For the relief of some of the inflammatory element, especially in intertriginous areas Neo-Cortef lotion or Cort Dome lotion is to be recommended. It is not possible as far as we know to inhibit sweating locally by the application of anticholergic preparations, but we have found in some patients that Prantal cream affords considerable relief from the pruritus experienced with sweating in the secondary miliaria of dermatitic skin. Topical as well as systemic treatment of any primary dermatitis is indicated and should be appropriately mild.

Systemic Treatment. Systemic treatment has no immediate effect, but some clinicians believe that vitamin A orally (50 000 I U aquasol capsules three times a day) or intramuscularly (100,000 I U in oil once weekly) will have a prophylactic effect. It would appear that there are rare cases of vitamin A metabolic defect in which miliaria may be the presenting sign [25] Others have espoused vitamin C as a defense measure against miliaria. Dosage here is empiric and again large (500 mg daily orally)

Radiation. X ray and grenz rays are without effect on miliaria. However ultraviolet light may be used prophylactically with benefit in some individuals. Peeling light exposures are generally poorly tolerated by miliarial skin although some cases may benefit.

PROPHYLACTIC MEASURES

Prophylactic measures of proved success center on all those factors which keep the skin dry and free from injurious agents. The miliaria prone must avoid dermatitis since they are the ones in which chronicity often appears because of the cycle of dermatitis → miliaria with pruritus → dermatitis. Hot humid environments must be avoided [26, 27] However it has been found that

in many people that as little as 8 hours a day in a cool or air conditioned area will be effective in reducing the ravages if not in preventing miliaria altogether [2]. It is the constant surface maceration 24 hours a day for 2 or 3 days which leads to keratinous plugging of the sweat pores and subsequent miliaria. The humid environment is especially troublesome, since the unevaporated sweat problem here is much greater than in warmer yet dry climates. Locally occlusive ointments must be avoided, since they invariably spell local miliaria in the susceptible. Adhesive tape is another cause of miliaria in some. It is well tolerated in winter but in summer a local tape reaction develops. This is often simply miliaria due to poral occlusion. It must be distinguished from the allergic eczematous contact dermatitis. Scotch tape or short periods of taping (less than 24 hours) may avert this tape miliaria. Finally, compresses and baths must be kept to short periods, since long exposures can lead to epidermal damage and miliaria.

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Daniel J Perry

14

ECZEMATOUS ERUPTIONS

ANY DISCUSSION OF eczematous dermatitis should begin with some clarification of what is meant by the term. It is derived from the Greek word *ekzema* (*ek* meaning "out" and *zeo* meaning "boil") and refers to the oozing, or weeping, which is found in the most active (acute) stage. Von Hebra was once reported to have said, "Eczema is that which looks like eczema." There is no universally accepted definition, because it has different connotations in different countries. In the acute state the predominant signs and symptoms are edema, erythema, vesiculation, oozing, crusting, and scaling. The less active or chronic, stage is characterized by lichenification (thickening) fissuring, scaling, hyperpigmentation, and excoriation. The acute state may rapidly or slowly undergo a transition to the chronic phase. The disease occurs in multiform patches and plaques. It is characterized by remissions and exacerbations. Itching and burning are the most aggravating symptoms. For purposes of this discussion the terms *eczema*, *acute* and *chronic dermatitis*, and *eczematous dermatitis* will be used interchangeably because they refer to the same disease process. Using weeping as a common denominator the entities infectious eczematoid dermatitis eczematoid dermatitis,

contact eczema, stasis dermatitis, exudative neurodermatitis, etc., are included.

The basic physiologic enzymatic, and immunologic changes occurring in eczematous dermatitis are not clearly understood, and their classification requires intensive investigation. Since the report by Stokes, Lee, and Johnson in 1943 [1] there has been increasing interest in the concept that eczematous eruptions might be caused by a variety of factors. Stokes, broadening this idea into a "factorial analysis, felt that each eczematous problem should be investigated thoroughly in an attempt to determine which factors appear to play a role in producing the dermatitis This approach helped to understand eczematous problems *wherein a trigger factor clearly seems to be important causatively* However appropriate treatment of this is not followed by a prompt disappearance of the disease. This is explained by the addition of secondary elements to the problem which appear to enhance or perpetuate the process. Eczematous problems of the hands in housewives are a common example, because detergents or cleansing agents frequently appear to be important causative factors. However the use of protective measures is not always followed by a disappearance of the disease. In these instances secondary factors must perpetuate the problem.

CAUSES

The various causes which are considered to play either a primary or secondary role in eczematous problems are usually divided into two major groups predisposing and precipitating.

Predisposing

The general physical status of the patient may be important. In instances of nutritional failure xerosus, pellagra, and cheilitis might precede eczematous changes. The possible role of liver damage in eczematous dermatitis has been discussed by Ayres, et al. [2] Hurlez et al [3] found abnormal liver changes in eczematous patients studied with liver biopsies.

People with abnormally dry skin are more likely to develop eczematous dermatitis. The use of soap in these persons increases

the dryness, producing itching and fissuring, which in turn can be followed by the eczematous picture.

Excessive sweating produces maceration which might be followed by dermatitis. It can also produce plugging of the sweat gland orifices with the subsequent development of miliaria as demonstrated by the studies of Shelley [4, 5] If many sweat glands are plugged and the environment is warm, itching, scratch dermatitis, and pustular miliaria might develop. This may become pyramided into a persistant inflammatory reaction.

Exciting

Contact (allergic) factors are probably the most important single cause of eczematous dermatitis. Rostenberg [6] defines an allergic eczematous reaction as one where a substance is not irritating on the first exposure but which in persons of appropriate genetic constitution causes the development of *sensitization* of the delayed type, so that subsequent contact with concentrations that are nonirritating to unexposed or nonsensitized persons produces an allergic reaction. This means that thousands of substances encountered in industry households, gardens, etc are potential sensitizers to many people Another large source of allergic eczemas is local treatment. Many times a simple inflammation of the skin is converted into a chronic one by the injudicious use of local or systemic therapy In dermatitic skin the stratum corneum is often partially or completely lost and promotes easier accessibility of chemical substances to the dermis In addition to this break in the mechanical barrier the patient with dermatitis is more likely to become allergic to agents which ordinarily have a low sensitizing index

Primary irritants include the large variety of solvents, detergents, soaps, and cleansing agents used in the household and in industry Primary irritants act in a manner different from allergic reactions. They produce an eczematous response by nonimmunologic means Rostenberg [6] describes two types The immediate type is the usual one where the eczematous reaction follows the first exposure The cumulative type requires repeated exposures

Mycotic infections may produce eczematous dermatitis. Yeast

infections with monilia are fairly common, particularly in housewives whose exposure to moisture and detergents can predispose to such infections. Pathogenic fungi can rarely cause an eczematous problem. Its incidence, however is less than 0.5 per cent. Some distinction must be made between the latter and a dermatophytid reaction. The "id" is secondary to a primary fungous infection elsewhere on the body The fungus can be isolated from the primary source such as the feet or groin, however the secondary or "id" site, has negative reaction in fungous cultures. The incidence of the dermatophytid is debatable. There is no controversy over the acute vesicular "id" which disappears in a short time when the primary area is cleared. However there are some who maintain that "id" reactions commonly precede an eczematous problem. This is a difficult point to assess clearly because it is not possible to tell definitely when an eczematous change actually begins. Certainly few chronic eczematous eruptions of the hands disappear when the primary site of mycotic infection is clear This persistence could, however be explained by the addition of other effects

Bacterial infections may be a primary or secondary factor in eczematous dermatitis. Livingood and Mullins [8] describe primary infections as those which are considered to originate in previously healthy skin This includes ecthyma, impetigo and furuncles. In secondary infections the organisms might not play a leading role in initiating the disease but may be important in prolonging or intensifying it The preexisting disease can be a laceration, burn, abrasion, contact dermatitis, fungous or virus infection, bites, drug eruptions, etc.

Mechanical trauma from garters, corsets, trusses, etc., can precipitate eczematous reactions through constant rubbing.

Physical factors such as heat and light can be related to eczematous problems. Sometimes the intense heat encountered in a blast furnace can play a role directly or indirectly through the production of a miliaria reaction. Eczematous dermatitis is one of the morphological types discussed by Lamb [9] in his study of light-sensitive dermatoses.

Vascular impairment in the arterial or venous circulation can

produce eczematous dermatitis. Stasis eczema is the typical example. It is considered to be caused by insufficient closing of the valves in the venous tree resulting in impairment of blood flow and oxygenation.

Food allergy may occasionally cause eczematous dermatitis. Rowe [10] Flood and Perry [10] and Winston and Sutton [12] have been instrumental in reviving some interest in this problem in recent years It is difficult to evaluate this factor because there is no ideal method for testing Scratch or intradermal allergy tests are of no value. This leaves various types of elimination diets or a strict trial diet which precludes all food for a short period This problem has been reviewed by Perry [13]

The possible role of inhalent allergens in the eczematous picture has been mentioned for many years. Recently Jillson [14, 15] has revived some interest in this problem by his studies of the relationship of inhalent allergens and molds in eczematous eruptions.

Drugs such as antibiotics, sulfonamides, diuretics, heavy metals, local anesthetics sedatives, and tranquilizers can cause eczematous dermatitis when used locally orally or parenterally

Neurogenic factors are an important cause of eczematous dermatitis. Some authorities consider the role of stress and its effect on the autonomic and central nervous system as the most important causative factor in producing this type of dermatitis. Others say it is not as important as other factors such as contact and primary irritants. It is difficult to determine how frequently neurogenic factors are important. They might be primary or secondary In the latter instance another agent can produce an eczematous problem. However the symptoms and morbidity can be so aggravating as to permit neurogenic elements to enter the picture as a contributing factor

The preceding discussion indicates that eczematous dermatitis can be produced by many factors acting alone or in combination. Clinically the eczematous skin looks the same regardless of the cause consequently each patient should be investigated from an etiological standpoint Certain factors which might play a role are often evident from a careful history This might indicate that

systemic, allergic, traumatic, mycotic, bacterial, or physical factors should be evaluated first. Careful examination might suggest that bacterial, mycotic, vascular allergic, or systemic factors require consideration. Based upon the history and examination, certain causative possibilities are suggested. These are then studied with the appropriate cultures, patch tests, blood or urine tests, etc., which are indicated. These studies require time and during the period of investigation intelligent and well-directed local and/or systemic therapy will aid greatly to relieve the patient of the symptoms and help the eczematous dermatitis become quiescent.

TREATMENT

Local

When one is confronted by the large number of therapeutic agents advocated for local treatment of eczematous dermatitis, it is a problem to decide what to use. Generally speaking, the most important concept is to do no harm. Pillsbury [18] has listed three main aims of treatment:

1 To provide some protection to the damaged tissue until the acuteness subsides.

2 To prevent excessive accumulation of debris resulting from oozing, scaling, and crusting without disturbing normal tissue.

3 To relieve itching as much as possible.

One of the major problems in local therapy is to know what type of agent to use at the appropriate time. The application of lotions and compresses is most effective in the acute stage. Here ointments would be washed away by the weeping. In the chronic stage lotions and compresses are too drying and ointments and pastes are best tolerated. A schematic diagram illustrating what agents are best tolerated in the different stages of eczematous dermatitis is shown in Fig. 14 1

Some useful wet dressings are U.S.P. Burow s solution (1:16 to 1 32) Domeboro tablets or powder (1 20) physiologic saline, or milk. Boric acid is still widely used, however in recent years there has been increasing evidence of possible absorption and

intoxication. This is more likely to occur in the acute stage of eczematous dermatitis when large areas are involved. Because of the potential hazard, it is not advisable to use boric acid in infants and young children.

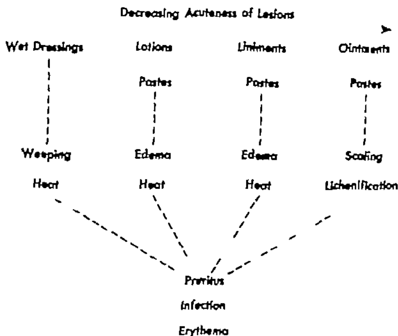


Fig. 14-1. General principles in topical therapy. (M. R. Lerner and A. B. Lerner. Dermatologic Medications, Chicago, Year Book Publishers, 1954.)

Many different types of lotions have been advocated in acute eczematous problems. They range from calamine lotion or its variants to local anesthetic or antihistaminic lotions. Some of the newer topical anesthetic agents include Tronothane and Quotane both of which are chemically unrelated to other anesthetics. At the present time there appears to be less danger of cross sensitization with them than encountered with procaine and its derivatives. *Topical application of antihistamines in lotions (or ointments)* has been widely used. The effect is nonspecific and is

thought to be due to the local anesthetic effect of these drugs. In this way it has an indirect antipruritic effect They are of some value in some eczematous eruptions, however they have a fairly great tendency to sensitize people [17] Local use does not appear to have an antihistaminic effect [18]

Figure 14 1 indicates that liniments, pastes, and ointments should be used as eczematous reactions subside. Liniments are lotions containing oil therefore they are less drying. Ointments are semisolids containing oily substances. Pastes contain 20 to 50% powder and the remainder ointment. Pastes adhere well to the skin and do not appreciably interfere with sweating.

In eczematous dermatitis soap is often not well tolerated con sequently a number of substitutes have been advocated. There are two main types of preparations which have been recommended First, there is the superfatted soap of which Basis is an example Secondly there are detergents or soaps with a pH lower than 7 The common examples of the latter are Lowila and Dermolate- of the former Phisoderm or Phisohex. These must be used carefully because they emulsify fats and can produce dryness. It is generally agreed that commercial soap changes the normally acid pH of the skin, at least for a time, to an abnormally alkaline state. Therefore, soaps and detergents have been blamed for many instances of eczematous dermatitis. Jambour and Suskind [19] however found no specific reactions to patch tests with a variety of commerical soaps and detergents, indicating that this question requires further study

The problem of protecting the in volved areas from further contact with causative allergic or irritant factors is an important one In instances of hand eczema, the use of rubber neoprene or plastic gloves may be of value The benefit of these gloves is augmented by the use of an inner cotton lining. Immersion of the gloved hands into hot water can produce considerable sweat ing, which is annoying to the housewife This can be absorbed by the cotton lining or a drying powder Since gloves can be annov ing, many types of protective ointments have been advocated. In recent years Silicone-containing ointments and lotions have been introduced. However there is some disagreement about the

efficacy of these preparations. Suskind [20] has reported that such agents are valuable in preventing industrial dermatitis. Morris [21] however found them to be of little value. In another study of these preparations, Kerodex, petrolatum, and various types of vanishing creams, Shaw and Crowe [22] found vanishing cream and petrolatum approximately as effective as the Silicone and other so-called protective preparations.

Bacterial infections frequently play a role in eczematous dermatitis, as previously mentioned. There are certain general principles in the management of these infections which have been advocated by Livingood et al. [8]

1. It is important to make the skin as inhospitable as possible to pathogenic bacteria. This can be aided by maintaining the skin in a dry state and avoiding mechanical or chemical irritation. An underlying eczematous dermatitis must be treated properly and potentially sensitizing agents should be avoided in topical therapy.

2. Cleansing and degerming of the skin, by simple measures, is *just as important as any specific antibacterial medication.* Soap and water and bland compresses are valuable. Soaps containing hexachlorophene are helpful, however recently there have been reports of allergic reactions to this. These simple measures can help to manage successfully 75 to 80 per cent of primary superficial infections of the skin.

3. When topical antibacterial agents are employed, it is generally inadvisable to use a compound which might be used systemically later for an internal infection. Therefore, antibiotics such as *sulfonamides, penicillin, streptomycin, Aureomycin,* Terramycin, erythromycin, or Achromycin are not recommended. Bacitracin, neomycin, and gramicidin are all excellent antibiotics. They have a low sensitizing capacity and are not often used internally. Bacitracin alone will not affect enough of the bacterial strains found in the skin. Consequently it has been combined with neomycin. This mixture has a wide enough antibacterial spectrum for most purposes.

Steroids. Since the introduction of cortisone in 1949, a number of chemically related derivatives have been available for study

Cortisone itself was of little value topically because it was not sufficiently active locally Hydrocortisone became available in 1951 and proved to be a very valuable adjunct to the local management of eczematous problems. This fact has been substantiated by many reports including the controlled studies carried out by Witten et al. [23] Apparently it is clinically effective in many different types of bases. Kalz and Scott [24] showed it to be therapeutically active in bases which were oily water repellent bases, hydrophilic emulsions, water in oil emulsions, oil in water emulsions, or oil free bases. These authors studied 284 patients and reported that the greasiest and dryest bases were the poorest performers. They concluded that the difference of therapeutic action of hydrocortisone in different vehicles is not determined by the influence of the base on the penetration of the hormone but by the compatability of the base with the disease and its location. The question of systemic effects from topical hydrocortisone has also been the subject of considerable investigation. Smith studied this problem and found no change in the circulating eosinophil count [25] or urinary 17-ketosteroids [26] after inunction of the ointment. Scott and Kalz [27] found some absorption when radioactive C 14 hydrocortisone was applied locally The consensus appears to be that if there is any absorption, it is not sufficiently great to affect the circulating eosinophil counts or ketosteroids in the urine. Originally hydrocortisone acetate and free alcohol were used however the more soluble forms, hydrocortisone diethylaminoacetate and hydrocortisone hemisuccinate sodium, were recently studied by Smith [28] He found that concentrations of 0.5% and 1% were not as effective as 1% concentration of the acetate or the free alcohol. This finding does not coincide with Welsh s observation with 0.5% hydrocortisone diethylaminoacetate [29] He concluded that this preparation (Magnacort) is more effective clinically in eczematous dermatitis than hydrocortisone alone

In 1955 another derivati e of hydrocortisone, 9-alpha fluorohydrocortisone (fludrocortisone) was found to be effective clinically in eczematous dermatitis. Wright et al. [30] reported that this compound possessed about 13 times the antiinflammatory

activity of hydrocortisone. Doses as low as 4 mg daily could control symptoms, however sodium retention, weight gain, increased blood pressure, and potassium depletion was observed. Fitzpatrick [31] also found an increase in blood pressure and weight in seven patients. He felt that a number of factors may be involved, namely the concentration, the site of application, the stage of the dermatitis, the extent and frequency of application. Florinef and Alflorone are two commercial products and are used in 0.1 to 0.2% concentrations. They are clinically quite effective and are probably safe to use in small areas of eczematous dermatitis in the chronic stage. However, it is advisable to watch for weight gain as a criterion of systemic effect.

In 1955 two new steroids were introduced, prednisone and prednisolone. The latter, used locally as a free alcohol, has been an effective antieczematogenic agent. One of the commercial products is Metiderm 0.5%. It is said to be substantially in solution and exerts its therapeutic effect without acting as an occlusive agent in the presence of an exudate. There is some evidence of absorption from topical applications. Tschan and Adoni [32] rubbed 0.5% into one-quarter of the body surface and found some decrease in the eosinophil count 4 hours later. Frank and Stritzler [33] reported that this compound was less effective than hydrocortisone and that it produced no sodium or fluid retention, potassium depletion, or hypertension. Robinson [34] reported it to be quite effective clinically. Further study will establish its relative therapeutic value among the steroid compounds.

Most of the steroids available for local use can be obtained with or without an antibiotic. When steroids were initially used, there was some concern that topical application would produce an overgrowth of pathogenic bacteria, yeast, fungi, or molds. This was considered because of the activation of tuberculosis attributed to the systemic use of steroids. There is no distinct evidence to date which indicates that topically applied steroids stimulate abnormal growth of organisms. Clinically in eczematous problems, when secondary infection is present, the combination of steroid and antibiotic such as neomycin can be quite effective.

It is also possible to use hydrocortisone and Vioform or oxyquinoline compounds (Quinolor or Sterosan)

Radiation

Since the advent of the atomic tests there has been increasing controversy about the use of radiation therapy because of the theoretical danger from the atomic fall-out. There have been many warnings of the theoretical dangers of radiation to the evolution of the human race. This has been carried to such a point that the public is beginning to question necessary diagnostic or therapeutic procedures. Radiation is a valuable medical tool as well as a potentially dangerous one in the hands of inadequately trained technicians. Somewhere between the extremes of not using radiation at all and using it injudiciously there is a happy medium where there are definite indications. This subject has been discussed by Crossland [35] who points out that dermatologists are using radiation therapy less frequently because newer methods have been developed which are replacing it in the treatment of many skin diseases.

Eczematous dermatitis is one of the diseases in which judiciously used radiation can be beneficial. It can give temporary or permanent relief to many patients suffering from this problem. There is no denying that harmful effects resulted from the earlier days of roentgen therapy when knowledge was limited. At the present time superficial roentgen therapy is quite safe when given by experienced specialists and by modern techniques [36] This was confirmed by Sulzberger et al. [37] in a follow-up of patients many years following radiation therapy They found no cancer or other sequelae in these patients from the Skin and Cancer Hospital in New York City

There are certain disadvantages to roentgen therapy in benign dermatoses. First of all, the total amount of radiation which can safely be given to any one skin area is 1,000 r given in divided doses. Secondly much of the superficial x-ray (half-value layer 0 5 to 1.0 mm Al) produces its ionization and therefore its biologic and therapeutic effects beyond the depth where pathologic changes are located in most benign dermatoses. Some of

these difficulties can be circumvented by the use of grenz rays (Bucky's rays) which are softer x rays (half value layer 0.018 to 0.036 mm Al) This form of radiation was first studied and utilized by Gustav Bucky and has been widely used in Europe and Scandinavian countries for many years. In recent years it has been gaining wider acceptance in the United States, because reliable calibration can now be obtained. Sulzberger and Baer [36] feel that the principle advantage of grenz rays over the more conventional superficial roentgen rays in the treatment of certain benign dermatoses lies in its greater safety Available evidence shows that the margin of safety in grenz ray treatment is many times that of conventional superficial roentgen therapy In situations where a total dose of 1 000 r should not be exceeded, the administration of grenz rays can be continued safely to much greater total doses. The sum of 30 years of experience has shown that grenz rays can be given up to a total of 1 600 r yearly to any one skin area over a period of several to many years without fear of producing permanent sequelae It is true that pigmentary changes and atrophy can be produced by huge doses of grenz rays (i.e. 40,000 r in one treatment) Pillsbury et al. [38] found no sequelae in 24 patients receiving 4,000 to 16,000 r in a single dose after a follow-up period of 9 to 56 months. In over 30 years of widespread use no malignant lesions due to grenz rays, as defined, have ever been proved to occur The greater margin of safety becomes more apparent when it is realized that this record has been achieved despite the difficulties and inaccuracies of dosimetry the unstandardized forms of apparatus, and the wide variability of ideas and techniques of therapy It is obvious that skin areas which have been treated with roentgen radiation before grenz radiation must be considered in a different category It is possible that grenz rays on areas previously treated with injudicial large doses of ordinary x-ray may produce serious results. This is a problem which has to be evaluated in individual cases. *Sulzberger and Baer [36] recommend* 100 to 200 r of grenz rays per treatment once to twice weekly usually up to a total of 800 r per course. Pillsbury et al. [38] advise 150 to 300 r Sometimes, as in the scalp Sulzberger and Baer [36] gave di ided

doses up to 1,600 r per course, and they found no instance of even temporary loss of hair occurring in any of the patients receiving this amount. Grenz rays are almost entirely confined to the extremely superficial skin layers and, in usual therapeutic doses, are not harmful to the hair roots, the eyes through the lids, or the testes through the scrotum. Thus they may be used in treating eczematous areas where roentgen rays are contraindicated. This does not mean that grenz rays are completely innocuous. The important drawbacks are:

1. The tendency to produce a much more intense local hyper pigmentation than do ordinary roentgen rays.

2. The relatively small size of the grenz ray field obtainable with most machines as compared with the fields which can be covered with ordinary superficial x rays.

3. It is apparently necessary to remove all local medication before using grenz rays, because Anderson et al. [39] showed that ointments such as zinc oxide transmitted only 34 per cent of grenz rays at 9 kv and 85 per cent of x-rays.

Sulzberger and Baer [38] believe that grenz ray therapy deserves increasing application as excessive doses produce only benign sequelae. On the other hand, in contrast to the well-known disastrous consequences from overdosage of ordinary x-rays, the occurrence of malignant changes after true grenz radiation has not been reported.

Systemic

Antihistaminics. Since the introduction of Benadryl and Pyribenzamine in 1945 many antihistaminic derivatives have been advocated. Increasing use of these compounds has indicated that they have a direct effect only on urticarial reactions. In eczematous dermatitis, which does not have an urticarial component, beneficial effects are limited to an unpredictable antipruritic effect. The mechanism by which this relief of itching is produced is not fully understood. Some investigators say that this is due to their sedative action. However there is no consistent correlation between amelioration of itching and soporific effect. Many patients who can hardly stay awake after taking one of the anti

histamines still have severe itching, while others have relief of itching but no sedative effect [40]

There are a multitude of compounds available today including Benadryl, Pyribenzamine, Hydryllin, Neo-Antergan, Phenergan, and Chlor Trimeton. There is little to choose between them in eczematous dermatitis, because they are only infrequently beneficial. Sometimes intramuscular or intravenous use will be helpful when oral administration is of little value. One reason why these drugs are sometimes ineffective clinically may be that the effect of single oral doses only lasts about 4 hours [41] This indicates that they should be given every 3 to 4 hours for maximum benefit. The newer long lasting compounds such as Perazil or Chlor Trimeton and the delayed acting compounds such as Pyribenzamine require further evaluation. On strictly clinical grounds it seems that the delayed acting drugs require more frequent administration than the recommended dose of one tablet every 8 to 12 hours.

Oral Steroids. The question of whether or not to use oral steroids in eczematous dermatitis is a controversial one There are some authorities who maintain that these compounds should never be used internally for such a chronic benign disease. Others feel that there are instances when they are indicated, however their criteria are not clear The disagreement lies in the fact that eczematous problems produce considerable morbidity but do not alter the life expectancy There is no doubt that eczematous dermatitis can ordinarily be substantially benefited by oral steroids However the disease usually relapses when steroids are stopped. In some instances there is a rebound reaction wherein the original disease is worse than it was preceding the use of steroids. The dangers of long term administration are well known. Therefore, in a chronic benign (from the standpoint of mortality) disease the use of oral or intramuscular steroids is something which must be decided on an individual basis.

If steroid therapy is used, cortisone hydrocortisone fludrocortisone, prednisolone and prednisone have similar morbidistatic effects. The sodium retention and edema from fludrocortisone has been mentioned previously [30 31] Smith [42] has compared the

activities of various adrenocortical compounds as illustrated in Table 14 1 Cortisone, hydrocortisone, and prednisone are comparable as far as fluid retention is concerned. The marked sodium retention of fluorohydrocortisone in contrast to the other three

Table 14-1 COMPARISON OF ACTIVITIES OF VARIOUS ADRENOCORTICAL COMPOUNDS

	Sodium retention	Interference with CHO metabolism	Antiinflammatory	Endogenous ACTH suppression
Cortisone	8	8	8	8
Hydrocortisone	10	10	10	10
Fluorohydrocortisone	1,000	250	250	250
Prednisone	12	32	32	32

Note Figures represent the relative activity of each compound with relation to the others in each area of activity; e.g., with regard to sodium retention, fluorohydrocortisone is 100 times more effective than hydrocortisone.

Source R. W Smith, "Uses of Cortisone and Its Derivatives, Lecture at American Academy of Dermatology Dec., 1955.

compounds is clearly shown Prednisone interferes more with carbohydrate metabolism and has more effect in suppressing endogenous ACTH metabolism than cortisone or hydrocortisone. Fluorohydrocortisone has by far the greatest effect in endogenous ACTH and interference with carbohydrate metabolism. It also has the greatest antiinflammatory effect, but the disadvantages prohibit its internal use. Sterane appears to have more anti inflammatory action than either cortisone or hydrocortisone. Brown and Clancy [43] Rein and Bodian [44] and Robinson [45] reported that at average therapeutic dosages prednisone and prednisolone do not disturb water and electrolyte balance. The usual morbidistatic dose of these is 20 or 30 mg initially with maintenance at a level of about 10 to 15 mg daily This is a lower dose than for cortisone or hydrocortisone The former usually ranges from 100 to 150 mg and the latter 60 to 100 mg. Tuberculosis, gastric ulcers (active or inactive) myocardial and renal problems are all considered to be contraindications to any steroid.

Tranquilizers. In recent years we have seen the advent of tranquilizers into the field of medicine. Since it has been well established that eczema can be due to anxiety emotional stress, and neurotension, this was one of the early diseases in which the effect of tranquilizers was studied. Many tranquilizing drugs, which differ widely in their chemical effects, have been introduced. They fall generally into four main groups

1 Rauwolfia alkaloids (reserpine) This is a pure crystallin alkaloid of the Indian shrub *Rauwolfia serpentina* Reserpine which was thought to be the most important of the serpentine alkaloids, was isolated in 1950. It produces a reduction of emotional response but does not have the narcotic or soporific effect of barbiturates. It is also supposed to produce a sense of well being and relaxation The mechanism of action is unknown, but Rein and Goodman [46] suggested that it acts on the hypothalamus and alters sympathetic and parasympathetic balance by partial suppression of sympathetic predominance In their study these authors report that 0.25 mg of reserpine four times a day was of some value in eczematous dermatitis. LeVan and Wright [47] reported more tranquilization and improvement in patients from reserpine than from placebo They felt that on the majority of patients it had a tranquilizing effect, but the degree varied from patient to patient. Unpleasant side reactions such as head ache vertigo oral dryness, nasal congestion, and depression limited its usefulness.

2. *Phenothiazines* (*chlorpromazine hydrochloride or Thorazine*) LeVan and Wright [47] studied the effect of 25 mg four times a day in a group of patients with conditions including eczematous dermatitis. They concluded, as with reserpine that on most patients these had some tranquilizing effect. However their usefulness is limited by the side reactions, some of which have been rather serious. Some of the undesirable effects are jaundice blood dyscrasias, photosensitivity [48] and cross sensitization with Phenergan The cross sensitization was observed by Sidi and Gervais [49] who found one of three people allergic to Phenergan cream were sensitive to Thorazine

3. Meprobamate (Equanil or Miltown) LeVan [50] studied

224 patients (including patients with eczematous dermatitis) who received 400 mg four times a day He felt that decreased anxiety and emotional stress were more consistent with Miltown than with reserpine or Thorazine. Side reactions were less frequent and included clouding of the senses and occasionally head ache or nausea. Sokoff [51] compared Miltown with phenobar bital and a placebo and concluded that phenobarbital patients had dullness of perception while meprobamate did not impair physical activity or mental alertness Allergic reactions to this compound reported to date consist of urticaria, erythroderma, exfoliative dermatitis, and erythema multiforme.

4. Hydroxyzine (Atarax) The recommended dosage is 10 to 25 mg three to four times a day LeVan considered it to be as effective as Miltown however more study is necessary to deter mine its usefulness. Side reactions such as headaches and dryness of the mouth have been observed.

From the available data all four types of drugs appear to have a tranquilizing effect in varying degrees in dermatologic patients. Tranquilization was evidenced by objective and subjective decrease of anxiety neurotension, irritability and emotional stress, and by the achievement of relaxation, improvement of sleeping habits, and sometimes a decreased pruritis. Individuals are said to be easier to manage, more cooperative and patient after the use of tranquilizing therapy [50]

Based on the consistency of response, the average degree of tranquilization, the frequency and severity of side reactions, LeVan feels that meprobamate and probably hydroxyzine are preferable as tranquilizing agents to rauwolfia and chlorpromazine. While the average doses have been stated, it is frequently necessary to increase the recommended doses to achieve the de sired results. He also suggests that therapy should be continued for at least 2 weeks before discarding a drug as not beneficial. It was often found that in the first 3 days of treatment there was drowsiness and lethargy but with continuation of these same dosages these symptoms diminished to tolerable levels.

If these ataractic drugs fulfill their early expectations, they will be a helpful addition to our therapeutic armamentarium. Any

thing which can be safely used and helps to relieve pruritus is an important adjunct. However there will still be eczematous patients who will not have subjective or objective relief from these drugs. Anything which will help to relieve itching in even a small group of these patients is welcomed. There is also the possibility that future drugs of this type will be more effective.

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Samuel Ayres Jr

15

OCCUPATIONAL DERMATOSES

SKIN DISORDERS constitute an imposing proportion of all occupational complaints. According to Schwartz, Tulipan, and Birmingham [1] reports from seven states indicate that about 5 per cent of all compensated occupational injuries are occupational diseases and that about 65 per cent of the occupational diseases are dermatoses. It has been estimated that the annual loss from occupational dermatoses in the United States is approximately 100 million dollars.

The early industrial compensation laws were concerned primarily with occupational accidents but later were gradually broadened to include diseases of occupational origin, thus drawing no distinction between an accident occurring at one point in time and a series of accidents occurring over a period of time and eventuating in a pathological condition or disease

Occupational dermatoses vary widely in their causes, the mechanism of their production, and their clinical appearances. The rapidly changing techniques of civilized life and the constant introduction of new chemical compounds into manufacturing processes and everyday living, to say nothing of the increasing

use of radiant energy offer a continuing challenge to the physician's detective ability

Clinically the eruption may vary all the way from slight dryness to eczematization, ulceration, folliculitis, pyogenic lesions, hyperkeratosis, malignant changes, atrophy scars, keloids and calluses, granulomas, and, in fact, practically any type of eruption encountered in the practice of dermatology

The emphasis in this symposium is on therapy rather than on diagnosis and cause, yet it is of course impossible to separate these three aspects of disease.

The treatment of any disease or symptom may be divided into two components, both of which are important (1) appropriate measures to give immediate relief of discomfort and (2) discovery and removal, if possible, of the cause to hasten the cure and to prevent recurrences. The first component is symptomatic treatment and the second might be designated as causal treatment. The latter is usually the more important, but in the private practice of dermatology it is frequently difficult to carry out, since so many skin disorders are of obscure causation.

In this respect, therefore, industrial dermatology has a decided advantage, since the nature of the patient's work usually furnishes clues as to the cause of his trouble and narrows down the causative possibilities. This is not always true however as is well illustrated by the case of a building inspector who presented an acute dermatitis of the face, neck, and hands which had every appearance of a contact dermatitis from some plant such as poison oak. The patient denied any possible exposure to poison oak or other plants; he lived in an apartment and had no house plants. Persistent questioning, however finally elicited the information that shortly before the onset of his eruption he had inspected a building which had a roof garden, and in the course of making his inspection he had come into contact with *Philodendron cordatum*, the vine with glossy heart-shaped leaves which is commonly trained over a moss-covered stick in a pot. A patch test with a philodendron leaf resulted in a strongly positive vesicular reaction.

Inasmuch as causal therapy or the discovery and removal of

the cause, is of such outstanding importance in industrial derma tology and is, under ordinary circumstances, fairly easy to achieve, it would seem appropriate at this time to consider some of the causes of occupational dermatoses, together with the corresponding clinical manifestations and symptomatic therapy

CAUSES OF OCCUPATIONAL DERMATOSES

I. Chemical
- *A.* Primary irritants such as strong acids, alkalis
- *B* Drying and defatting agents, such as water soaps, detergents, solvents
- *C* Contact sensitizers
  1. All the varied substances encountered in the customary performance of the patient s work
  2. Incidental substances not primarily concerned with the occupation
- *D* Internal toxic or allergenic agents such as fumes, poisons, medications prescribed for other occupational injuries or diseases
- *E.* Externally applied medications for other occupational injuries or diseases

II. Biological
- *A* Bacteria, chiefly secondary infections
- *B* Fungi, especially the yeast group
- *C* Viruses
- *D* Protozoa, including syphilitic gummas activated by trauma
- *E.* Animal parasites

III Mechanical
- *A.* Trauma
- *B* Foreign bodies (foreign body granuloma)
- *C* Friction or pressure causing occupational stigmata

IV Physical
- *A.* Light
  1. Sunlight
  2. Artificial ultraviolet light
  3. Ionizing radiations, such as ray adium, nuclear energy
- *B* Heat
  1. Excessi e perspiration such as miliaria, intertrigo
  2. Burns
- *C* Cold
- *D* Electricity

CONTACT DERMATITIS

Contact dermatitis is undoubtedly the commonest clinical manifestation of occupational dermatoses. The eruption is usually eczematous in appearance, consisting of various degrees of erythema, vesiculation, exudation, crusting, and occasionally lichenification, and sometimes complicated with secondary infection.

Such eruptions usually begin at the point of contact with the offending agent, but if the process is sufficiently acute, the eruption may also appear elsewhere because of the development of autosensitization by absorption from the patient's own altered tissue proteins. These eczematous eruptions may be extremely mild, consisting of no more than slight dryness or chapping, or they may be very acute with edema and confluent vesiculation.

Eruptions of this type are usually caused by chemicals ranging all the way from such simple things as water or metallic nickel, through the simple inorganic compounds of chromium, arsenic, calcium, etc., to the highly complex synthetic resins and other organic compounds.

Chemicals in industry may produce a dermatitis in at least three ways: first, by interfering with the normal protective mechanisms of the skin as in the softening of the keratin layer and the removal of the natural oils from the skin through the action of water, solvents, detergents, cleansing agents, alkalis, second, by exposure to strong chemicals which act as primary irritants and include many substances, and third, by contact allergic sensitization. While the latter probably constitutes the largest single group of industrial dermatoses, the fact must not be overlooked that many dermatoses are caused, not by the manufacturing processes to which the worker is exposed, but by the methods employed in cleaning the skin after work, including the use of solvents, strong soaps, detergents, and waterless cleaners.

The patient may also be sensitive to protective creams and rubber gloves and is very frequently made worse by injudicious

treatment. Sometimes the condition is aggravated by the development of an allergic sensitization to perfectly proper and ordinarily harmless local medication such as an ointment base.

The potential irritants to which people may be exposed in the course of work are practically unlimited but the nature of an individual's job usually narrows the list to workable proportions. A very much abbreviated list might include the following: dyes and other chemicals used in various fabrics, furs, and leather photographic, lithographing, and printing chemicals rubber soap, detergents, solvents, cosmetics, antiseptics, insecticides, cutting oils, linseed oil, essential oils of plants, natural and synthetic resins, glues, coal tar and its derivatives, explosives, including match heads, plasticizers, metallic nickel, chrome compounds, cement, sawdust certain plants such as poison oak, poison ivy *Primula obconica*, philodendron weeds and weed pollens.

Some of these irritants turn up in unexpected places. Chromium, for instance which is a common source of trouble, is found not only in electroplating and in the airplane industry where zinc chromate paint is used, but also may occur in cement, rust proofing solutions which are used in radiators of diesel locomotives and automobiles, tanned leather cutting oil etc. Morris [2] cites two cases of chrome dermatitis in workers handling glue which was made from scrap chrome-tanned leather

Fabrics may irritate not only because of dyes but also because of various finishes, resins, mothproofing, mildew proofing, and fireproofing preparations. Rubber is not usually thought of as a hazard among clerical workers, but the use of fingerstalls in leafing through reports and files, the habit of twisting rubber bands about the fingers and the ordinary eraser offer ample opportunity for the development of rubber dermatitis in office personnel

Klauder [3] cites a classic example of an irritant in an unexpected place, in the case of an electrician who had a chronic dermatitis of the hands, forearms, and face of a years duration, who failed to respond to treatment although he improved when away from work, and who showed negative patch tests to all

materials handled in his work. The cause of his trouble was suggested by the development of a perianal dermatitis after using a paper towel instead of toilet paper A patch test with the paper towel used at work gave a positive result. Four months were required for the disappearance of the chronic dermatitis of the face after discontinuing use of paper towels. There were no recurrences during the ensuing 10 years.

Nothing could illustrate better the importance of treatment based on cause than the history of this patient.

In addition to occupational contact irritants, it is also possible for the same type of eruption to result from exposure to irritants at home or in the course of hobbies.

The determination of the specific cause of the patient s eczema tous eruption must be based upon a detailed history and frequently requires persistent questioning on numerous occasions. Patch tests, properly performed, diluted when indicated and avoiding the testing of poisons or primary irritants may give valuable information.

Secondary complications must be carefully weighed, and these include irritation from treatment, gross secondary bacterial infection, or the less conspicuous secondary infections which not infrequently supervene and prolong disability far beyond a rea sonable expectation. Other complications include disseminated lesions or id" reactions from autosensitization, nervous and emotional factors from fear of losing a job preexisting systemic dis orders such as atopic diathesis, focal infection, anemia, nutritional and metabolic disturbances.

One of the commonest and most frequently overlooked complications is the use of soap, and the more aggravated the skin disorder the greater the tendency of the average layman to scrub with soap, on the theory that a skin disease is unclean or is due to an infection which must be washed away The idea of not using soap on inflamed skin is so automatic and instinctive to the dermatologist that he sometimes fails to realize that the average layman has entirely different ideas. Detailed instructions are important.

Symptomatic treatment of eczematous contact dermatitis will

depend a good deal upon the extent and severity of the eruption and the presence or absence of secondary infection.

Certain drugs have a bad reputation as skin sensitizers and should be avoided routinely including ointments and lotions containing local anesthetics, especially members of the caine family most local antihistamines, tars, mercury sulfathiazole sulfur penicillin, and strong antiseptics.

If the eruption is extremely mild, the patient may be permitted to continue work if he is able to protect himself from further exposure to the suspected irritant. In all other cases, it is our custom to advise the patient to remain away from work until the eruption has healed, or to do a different type of work which does not involve exposure to potential irritants.

The patient should be instructed to avoid soap completely on the affected areas and to use water sparingly Under certain circumstances, a soap substitute such as Phisoderm or Soy Dome cream can be prescribed. He should be advised to discontinue completely any prior medication or cosmetic cream or lotion. Unless specifically warned, patients will sometimes continue to use previous applications in addition to the medicine prescribed.

It is also the author's practice in all cases of inflammatory or infected dermatoses to carry out patch tests at the time of the patient's first visit with various topical medications including a number of ointment bases to preclude the possibility of prescribing anything to which the patient might be sensitive and thereby aggravating his condition. Until these patch tests have been observed at the end of 48 hours, the initial topical medication should be as simple as possible If the eruption is severe and extensive so that systemic steroid therapy is required, these preliminary patch tests are deferred, since the steroids would tend to suppress any positive reactions and render the tests of questionable value.

In a mild case of contact dermatitis of limited extent, the author frequently prescribes at the first visit an ointment or cream containing 1% hydrocortisone powder in a cold cream or vanishing cream base, depending upon whether the dryness of the skin requires lubrication. The author prefers the prescribed mixture

to the ready-made preparations for three reasons: It is usually less expensive, the base can be patch-tested, and the base can be varied according to the requirement of the skin. The only disadvantage is that many druggists do not have hydrocortisone powder in stock, but this can easily be overcome by prior arrangement with designated pharmacies. If the eruption is very mild or consists of chapping, a simple emollient such as a standard cold cream or Nivea cream or lotion may suffice. Topical hydrocortisone or related preparations should not be prescribed for extensive eruptions because of the prohibitive cost.

For the treatment of more acute eruptions, calamine lotion U.S.P. or continuous cold wet dressings of boric acid solution are still effective as well as inexpensive. The oral administration of antihistamines, especially the long-acting types, are often helpful. The nonspecific effect of Piromen injected subcutaneously appears to be beneficial, with a beginning dose of 0.05 ml and increasing by increments of 0.05 ml up to a maximum of 0.75 or 1 ml.

In very severe and extensive eruptions the cortisone derivatives such as prednisone and prednisolone are extremely valuable, and many brands are available. The author has used them in 5 *mg* tablets, prescribing six tablets a day for 2 or 3 days in divided doses after meals, and at bedtime, then reducing gradually over a period of 10 to 14 days. It is important that the dosage be tapered off gradually and not terminated abruptly because of the danger of a flare-up. The usual contraindications to steroid therapy such as hypertension and gastric or duodenal ulcer should be observed. Since most cases of contact dermatitis are self limited, the need for prolonged administration of steroids is unlikely; the possible side effects in the average case are minimal and are far outweighed by the prompt relief of discomfort and disability. Since the advent of steroid therapy the need for hospitalizing cases of contact dermatitis has, in our experience, practically ceased.

In those patients receiving steroids orally there is no necessity for the use of topical steroids. Calamine lotion, boric compresses, and later a bland cream, ointment, or paste, are adequate.

A useful paste for the later stages of an acute dermatitis or for a mild eruption is the modified 1-2-3 paste

℞		
	Dist. water	5
	Liq aluminum acetate	5/
	Anhydrous lanolin	10/
	Plain Lassar's paste	30/

Sig Apply b.i.d. and cleanse with olive oil or mineral oil.

Sterosan or Vioform cream, alone or containing 1% hydrocortisone powder are effective in the less severe eruptions. Both these drugs exert antibacterial and mild antifungal as well as anti inflammatory effects.

In the more chronic types of eruptions *with thickening or* lichenification, some of the milder tarlike preparations may be used such as the recently introduced Metashal ointment or lotion, one of the coal tar preparations or a Naftex paste prepared as follows

℞		
	Naftex	10/
	Zinc oxide	10/
	Corn starch	10/
	Petrolatum	20/

Sig Apply twice daily

Cole [4] reported success in treating chromium dermatitis both in experimental animals and in six patients by local applications of 3% BAL (dimercaprol) in a zinc oxide ointment A seventh patient could not tolerate the ointment.

The conservative administration of superficial x ray therapy by a physician especially qualified in its use in the subacute or chronic cases may hasten the disappearance of the eruption. It goes without saying that the question of previous roentgen therapy must be definitely established and that a maximum total amount of 15 doses of 75 r to any one skin area should not be exceeded and considerably less than that amount given if opposite surfaces of a part such as the hand or arm are treated.

The occurrence of eruptions from poison oak or poison ivy among workers in certain outdoor occupations is still a problem. Attempts at specific immunization have not proved too satisfactory Protective clothing, barrier creams, especially those designed

to protect against oils and solvents, and the use of chemical weed killers are probably the best measures. Immediate washing after known exposure sometimes prevents an attack of dermatitis.

BACTERIAL INFECTIONS

Bacterial infections of occupational origin include pyodermas secondary to trauma, furuncles from cutting oils, ulcers following injury erysipeloid in fish handlers, infectious eczematoid dermatitis or other low grade bacterial infections which supervene upon contact dermatitis.

The more serious bacterial infections should receive the benefit of systemic antibacterial therapy although sensitivity of the infecting organism should be determined as early as possible in order to secure the maximum benefit from such medication. It is of very little value to administer an antibiotic to which the bacteria are resistant. Abscesses and furuncles should obviously be opened and drained, crusts and pustules should be debrided. For localized areas a multiple antibiotic ointment such as Neosporin is effective. For more extensive involvement, continuous cool boric compresses or alibour water are valuable. The latter is prepared as follows

Copper sulfate	1/6
Zinc sulfate	5/6
Sat. sol. camphor	
Water	q.s. ad 240/

Sig Dilute a tablespoon to one glass of water as wet dressing.

In extensive but less acute infections boric acid ointment U.S.P is inexpensive and satisfactory when used in conjunction with systemic antibiotics.

Milder and subacute bacterial infections, especially those complicating contact dermatitis, respond well to Vioform or Sterosan cream with or without 1% hydrocortisone depending upon the degree of inflammatory reaction.

Local sulfonamide ointments are used much less than formerly because of occasional allergic reactions. Sodium sulfadiazine or sodium sulfacetamide ointment in 5% strength are often effective and rarely produce reactions. Five per cent scarlet red ointment

is valuable in stimulating the healing of sluggish wounds or ulcers.

Erysipeloid is caused by *Erysipelothrix rhusiopathiae* and usually occurs on the hands or fingers especially of fishermen, butchers, cooks, and meat inspectors. It usually responds to penicillin administered intramuscularly

Granuloma pyogenicum is a small vascular tumorlike excrescence with granulation tissue and slight pus or crusting which may follow trauma. It may require destruction under local anesthesia by electrodesiccation followed by 10% silver nitrate and a dry dressing with Aureomycin powder

A special type of bacterial infection occurs in conjunction with follicular plugging and irritation in some workers exposed to cutting oils. This eruption resembles acne vulgaris with comedos, papules, pustules, and sometimes abscesses, except for the fact that it may occur at any age and is usually limited to areas exposed to the oil, especially the forearms and the anterior aspects of the thighs where oil may soak into the trousers. The face, anterior aspect of the trunk, and genital areas are frequently involved. This condition is known as chloracne and is due to chlorinated hydrocarbons which are frequently present in cutting oils.

The treatment of this condition requires that the individual be removed from further exposure to cutting oil until the condition has healed, which may require a number of months Proper ventilation, shielding, adequate protective clothing, and scrupulous cleanliness would minimize the occurrence of this condition The eruption requires much the same type of treatment as ordinary acne, including opening and draining of pustules, expression of comedos, thorough washing with a mild antiseptic preparation such as a soap containing hexachlorophene or Fostex cream or cake, a sulphur lotion such as lotio alba, and superficial roentgen therapy carried out by a physician especially qualified to administer it. If the infection is severe an antibiotic based on sensitivity tests to the infecting organism, given for a period of 1 to 2 weeks, may bring the acuteness of the process under rapid control.

Syphilis, although not strictly a bacterial infection, and tuberculosis may be mentioned briefly under this heading. In patients with latent syphilis, trauma may precipitate the development of a gumma at the site of the trauma. Such cases have been considered as of occupational origin up to the point of curing the gumma by antiluetic treatment, which at the present time, of course, means penicillin. The insurance carrier would probably not be held responsible for the complete eradication of the syphilitic infection.

Tuberculosis of the skin of occupational origin could occur in laboratory workers who became accidentally infected.

FUNGOUS INFECTIONS

The commonest fungus encountered in industrial dermatology is *Candida albicans* formerly known as *Monilia*, a member of the yeast group. Since excessive exposure to moisture and sugar favors the growth of this fungus, it is found most commonly on the hands among people who are employed in wet work, such as dishwashers, cooks, canners, fruit and salad handlers, and candy makers. Its two principle manifestations are erosio interdigitalis and chronic paronychia, and they frequently occur together. In the former there is an erythematous, glazed, macerated, and fissured appearance in one or more of the finger webs and on the opposing surfaces of the fingers; in the latter the nail folds are reddened, swollen, and separated from the nail with or without pus formation beneath the nail fold. The nails of the involved fingers are frequently ridged and dystrophic, either because of interference with normal nail growth or from actual invasion of the nail with the fungus.

The new antibiotic fungicide Mycostatin is specific for this fungus and is usually promptly effective in ointment form. It may be alternated with fungicides containing undecylenic or propionic acid derivatives, Castellani's carbol fuchsin dye, or an ointment containing sulfur and salicylic acid in a strength of 5 to 7% of each.

It goes without saying that every effort should be made to protect against exposure to water or other substances which favor

the growth of the yeast fungus. Prolonged wearing of rubber gloves is not the answer since the hands are then macerated with perspiration. Protective creams may help, but a change of occupations may be necessary. Infected nails should be ground with a dental bur to facilitate contact with the medication.

Intertrigo involving the large flexural folds may be due to *Candida* or to bacterial infections supervening upon excessive perspiration and may be considered to be of industrial origin when a person's occupation requires him to be exposed to conditions of excessive heat and humidity. A change of occupation may be necessary to obtain a cure. In those cases in which *Candida* can be demonstrated by direct examination or by culture, Mycostatin ointment is usually effective. For those of bacterial origin, Sterosan or Vioform cream or Neosporin ointment are valuable.

Inasmuch as sugar favors the growth of *Candida*, the possibility of an underlying diabetes should be ruled out in all cases of moniliasis.

Infections with other species of fungi are seldom of occupational origin unless the nature of the patient's work brings him into contact with the infecting organism, which therefore must be determined by culture. People handling animals, teachers exposed to infected children, workers sent into an area where an infection is endemic, such as coccidioidomycosis in San Joaquin Valley, would be exceptions. In addition to coccidioidomycosis, other deep fungous infections such as blastomycosis, sporotrichosis, and actinomycosis are occasionally of occupational origin, depending upon the nature of the patient's employment.

VIRUS INFECTIONS

Vaccinia, or cowpox, may be acquired by milkers from infected cows' udders. The lesions resemble those following smallpox vaccination. Milkers' nodules result from a different virus and are also acquired in the process of milking an infected cow. Sheep pox, or orf, is another virus disease, usually consisting of a single bean-sized or larger inflamed papule which becomes umbilicated, pustular and granulomatous, healing spontaneously. All these

conditions are self limited. Alibour wet compresses or Neosporin ointment tend to minimize secondary infection.

ANIMAL PARASITES

Several species of *Sarcoptes* which are related to the mite causing human scabies, attack animals such as dogs, cats, pigs, and chickens and may be transmitted to persons working in close contact with infected animals. The mites of animal scabies frequently attack the head and face in human beings, contrary to the habits of the human sarcoptes.

Mites from cheese, dried fruit, grain etc., may also occasionally attack human beings. In most instances the infestations from these various mites do not persist. The treatment is the same as for human scabies and one of the most effective and least objectionable agents is Kwell ointment applied to the entire body for 3 nights. The clothing should be sterilized or dry cleaned.

DERMATITIS MEDICAMENTOSA

When eruptions result from either the local or systemic treatment of industrial injuries or occupational diseases then these secondary eruptions automatically become industrial dermatoses.

Probably the most frequently encountered eruption of this type is the acute eczematous dermatitis superimposed upon a cut, scratch, or abrasion or upon a preexisting occupational dermatitis resulting from the application of local medication to which the patient was hypersensitive. This has already been dealt with in the discussion on contact dermatitis.

Not infrequently medication given orally or by injection may also produce allergic reactions. The commonest offenders are tetanus antitoxin and penicillin, both of which tend to produce urticaria or angioneurotic edema. These eruptions may persist over a period of a few days to many weeks, especially in the case of penicillin. Persons highly sensitive to penicillin may be adversely affected by traces of penicillin in milk derived from cows which were treated by penicillin for infected udders, or by related molds found in certain brands of cheese.

Very acute cases of urticaria or angioneurotic edema may also

develop severe asthma or edema of the glottis with strangulation and deserve the benefits of prompt steroid therapy with one of the prednisones or prednisolones in a dose of at least six 5 mg tablets given in divided doses four times a day gradually reducing the dose over a period of 10 to 14 days. ACTHAR HP Gel in a dose of 60 I.U may be given intramuscularly at the first visit and repeated every other day for a few times in gradually descending doses.

In less severe cases, an *immediate intramuscular injection* of 0.5 ml of adrenalin in oil (1 to 500) will give prompt relief This may often be maintained by the oral administration of one of the many available antihistamines, especially the long-acting type Piromen, which was mentioned above in connection with the treatment of contact dermatitis, is also of some value and the author feels that there is some virtue in the administration of calcium intravenously either in the form of calcium ascorbate 5 ml or calcium thiosulphate 5 ml given at intervals of 3 or 4 days.

Topical applications are of questionable value in the treatment of urticaria. Either calamine lotion U.S.P or the following may help

Phenol	2
Talc	25
Corn Starch	25
Glycerine	20
Magma benonite	100
Dist. water	q.s. ad 240

Sig Apply for itching.

There is practically no drug which may not at some time and in certain individuals produce eruptions, varying all the way from urticaria to erythema multiforme fixed eruptions, exfoliative dermatitis, and even pustular pemphigoid, or *granulomatous* lesions, as in the case of iodides and bromides.

It is impossible in the scope of this discussion to outline treatment for all these various possible eruptions. The first essential in the treatment of such cases is a high index of suspicion and the exclusion of *all possible offenders. Local or systemic therapy* would have to be fitted to the clinical manifestation presented

SYSTEMIC POISONS

Various chemicals ranging from such metals as arsenic and mercury to solvents such as carbon tetrachloride and the newer insecticides may produce dermatoses either directly by toxic injury to the skin, by sensitization mechanism as exemplified by exfoliative arsenical dermatitis, or by indirect means as a result of injury of other organs, as for instance a nondescript pruritic or eczematous dermatitis resulting from liver damage from the inhalation of fumes.

The treatment would vary with the mechanism involved. In exfoliative dermatitis from arsenic or mercury the administration of BAL (British anti-lewisite, 2,3-Dimercaptopropanol) hastens the elimination of the metal from the tissues. It is injected intramuscularly in a 10% solution, in a dose of 3 mg per kilogram of body weight, every 4 hours for the first 2 days, four injections on the third day and twice daily for 10 days or more as needed.

In addition steroid therapy would bring about prompt symptomatic relief while the BAL was in the process of eliminating the cause Locally a bland lubricant such as mineral oil, Nivea oil, or a simple cold cream would relieve the dryness.

Dermatoses secondary to liver damage as revealed by liver function tests might be helped by liver supporting therapy including a high protein, low fat diet, crude liver extract intramuscularly and high potency vitamin B complex with C and a lipotropic agent such as Methischol orally

FOREIGN BODY GRANULOMAS

Foreign bodies which have become embedded in the skin over a period of time have a tendency to set up a granulomatous type of reaction which may simulate a variety of clinical entities such as a deep fungous infection, tuberculosis, neoplasm, or a draining sinus. Various objects such as metallic, wood, or glass splinters, sand, thorns, cactus spines, and short-clipped hairs may initiate the process. Barbers are particularly susceptible to granulomas or sinuses in the finger webs from customers hairs.

The only effective treatment is removal of the cause which can

be done under local anesthesia either by extracting the foreign body or excision by the knife or the cutting current of the entire lesion containing the foreign body Destruction by electrodesiccation and curettage would be effective but would preclude identifying the foreign body unless it had been found previously by biopsy

SCARS AND OCCUPATIONAL MARKS

Various types of injuries, and especially burns, may be followed by unsightly scars which require treatment for cosmetic reasons or because of impaired function or discomfort Large, thickened scars which restrict motion are in the province of the surgeon. Hypertrophic scars and keloids, which are thickened scars that continue to grow should be treated. Surgical removal alone is likely to be followed by recurrence and an even larger scar Lightly filtered fractional roentgen therapy is frequently effective Techniques vary but I have been accustomed to administering 150 r with 1 mm aluminum filter closely shielding the surrounding normal skin, and repeating at approximately 2 week intervals for a total of up to 10 treatments if needed.

More recently the injection of hydrocortisone directly into the thickened scar tissue has been found to be of considerable benefit. An injection of a saline suspension of hydrocortisone acetate especially prepared for such use must be made through a dental syringe and should be preceded by infiltration of the surrounding tissues with a local anesthetic. Injections may be repeated at intervals of 2 to 3 weeks.

If the scar is markedly thickened, it may save time to shave off the elevated portion flush with the surrounding skin under local anesthesia, following with an application of silver nitrate stick and an injection of hydrocortisone into the base of the lesion or the immediate institution of roentgen therapy as described above

Pitted scars and depressed or uneven linear scars may be greatly benefitted by surgical planing using Freon 114 both as a local anesthetic and an agent for rendering the skin firm to facilitate the abrading technique Ronchese has written numerous enlightening articles on occupational marks which are char

acteristic of certain trades. The reader is referred to his comprehensive chapter on occupational marks in the new edition of "Occupational Diseases of the Skin" by Schwartz, Tulipan, and Birmingham [5]

SUNLIGHT AND OTHER SOURCES OF RADIANT ENERGY

Aside from the normal erythema from excessive exposure to the sun, some persons are hypersensitive to actinic rays from the sun or from artificial sources of light. Such individuals whose work requires daily exposure to the sun as farm workers, laborers, fishermen, and seamen may be quite incapacitated and may have to change to indoor work.

Polymorphic light eruptions which are usually limited to exposed areas, and lupus erythematosus, both of the chronic discoid and the more serious systemic types, are the more frequently encountered manifestations of light sensitivity. The former and porphyria cutanea tarda are often associated with impaired liver function. Patients with clinical or subclinical pellagra are also usually light-sensitive.

If avoidance of exposure to light is impractical, some benefit can be achieved by applying one of many available sun screening lotions or creams, although they in turn may occasionally produce allergic reactions. The antimalarial drugs are frequently beneficial in reducing sun sensitivity. Chloroquine in a dose of 250 mg twice daily for 1 week, then once daily may afford reasonable protection while it is being taken. Calamine lotion U.S.P. or 1% hydrocortisone lotion or cream are suitable local applications. Attention should be directed to possible underlying systemic disturbances such as focal infection, impaired liver function, nutritional anemia, and alcoholism.

People who are light-sensitive may also break out from artificial sources of light such as fluorescent lights used in offices and stores.

Contact with certain chemicals such as tar of various types, colognes, and some plants may render normal skin hypersensitive to sunlight or artificial ultraviolet light.

Long-continued exposure to sunlight in fair-skinned, nontan-

ning individuals may after a period of years lead to the development of actinic or senile keratoses and epitheliomas. Similar changes can be produced in a much shorter period of time following excessive exposure to x rays or other sources of ionizing radiation such as the newer developments in the atomic energy field. Superficial keratoses can be destroyed by freezing with liquid nitrogen or solid carbon dioxide, while the thicker ones should be destroyed by excision or electrodesiccation followed by curettage. Epitheliomas can be successfully removed by excision with the knife or cutting current, thorough electrodesiccation and curettage or by radiation (except those caused by radiation) depending upon the size, location and type of the lesions.

Chronic ulcers due to radiation injury which have not progressed to actual malignancy may sometimes be stimulated to heal by 5% scarlet red ointment or Neosporin ointment or by the application of the pulp of *Aloe vera* leaves.

In cases of chronic radiodermatitis with dryness, fissuring, and atrophic changes, the author has gained a clinical impression that the use of vitamin A ointment containing Cytomel (1-triiodothyronine) in the proportion of 50 to 100 μg to 30 gm of ointment has given some degree of relief

Acute radiodermatitis is treated like a sunburn with calamine lotion or 1% hydrocortisone in a liquid or vanishing cream base

BURNS

Dermatologists are seldom called upon to treat patients with burns, inasmuch as such cases are usually either sent directly to emergency hospitals or are seen immediately by general practitioners or surgeons.

Small superficial first or second degree burns are usually relatively simple problems. Calamine lotion U.S.P or 1% hydrocortisone in a vanishing cream base reduces inflammation and relieves discomfort. The addition of an antibiotic minimizes local infection. Cold boric acid wet compresses or cold compresses with liquor aluminum acetate diluted 1 to 20 are useful.

For more extensive burns, Pendleton [6 6a] advocated a paraf

fin spray mixture which after melting in a water bath is sprayed directly on the burned areas with an ordinary insecticide spray gun. The preparation is made up as follows:

Paraffin wax (household wax, melting point about 125 F)	670 gm
Petrolatum	250 gm
Liquid petrolatum (heavy)	150 gm
Cod liver oil (or cottonseed or olive oil)	50 ml
Sulfanilamide powder (other sulfonamides can be substituted)	50 gm
Menthol	1 gm
Camphor	1 gm
Oil of eucalyptus (deodorant)	1 ml

Pendleton cited the following advantages of his spray technique

1 It can be used on the face, scalp, neck, genitalia, hands, easily constricted areas like the arms and legs, and around the eyes, lips and nares. It has been used on all types of burns.

2. It stops pain instantly thus preventing early shock from pain and providing comfort throughout healing The mechanical covering of the tiny injured nerve endings probably accounts for the dramatic cessation of pain.

3. There is no absorption of sulfanilamide into the blood, therefore it can be used by laymen, first aiders, nurses, and doctors without fear of reactions.

4. It prevents trauma (from frequent dressings) to the tender epithelial cells which normally spread from the sweat glands and hair follicles out over denuded areas. This allows earlier healing, lessens scarring, and avoids most plastic repairs

5. Other injuries or infections may be detected because there are no bulky dressings to remove. (*Every burned patient should be seen by a doctor every day until healed.*)

6. It is inexpensive, easily mixed, and may be used in isolated battle stations with little equipment and no trained personnel.

7 Dressing time is reduced 90 per cent over most methods, because no gauze is required.

8. Early body motion is possible and encouraged, because there are no restraining, traumatizing bandages.

Early frequent tap water flushings and showers remove secre-

There are a great many types of these protective creams, some of which are much more effective than others. Some are designed especially for protection against water and water soluble substances, while others are effective against greases and solvents. These preparations should not be applied over active eruptions. Occasionally these prophylactic agents may themselves set up an irritation, after having been used for a certain length of time. Allergic contact sensitization may develop from any of the barrier creams, from leather gloves, or from natural or synthetic rubber gloves, or even from a glove powder. Various cleansing agents if applied too vigorously and especially certain brands of waterless cleaners and solvents to remove grease, are frequent causes of dermatitis. Occasionally the protective clothing will set up an irritation. Sun protective creams, and various creams and lotions to protect against dryness, especially those containing lanolin or lanolin derivatives, are occasional offenders. The possibility of sensitization to paper towels and to deodorizing sprays and insecticides used at the patient's place of employment are not to be overlooked.

In conclusion, it should be emphasized again that the treatment of occupational dermatoses does not differ from the treatment of skin diseases in general, since occupational dermatoses do not constitute any sort of a clinical entity but overlap practically all branches of dermatology. The most important part of the treatment is in the detective work involved in tracking down the culprit.

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Thomas H Sternberg
and Victor D Newcomer

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ATOPIC DERMATITIS

In several previous reviews the authors have summarized the fundamental principles involved in the treatment of atopic dermatitis [1 2] These are all nonspecific in nature, although many are directed toward the elimination or modification of precipitating, or trigger factors Conservatively it can be stated that the management of atopic dermatitis from infancy through adulthood is one of the most perplexing and trying problems in medicine and is likely to remain so until a better understanding of the basic physiopathology is obtained.

The infant or child with a severe atopic dermatitis presents a dual problem, namely the treatment of the patient, *per se* and the management of the disruption of the family routine as the result of the patient's illness. The long duration and expense of treatment, the amount of time necessary for the daily care and the numerous sleepless nights on the part of the family soon create in the parents either a feeling of desperation or a veneer of indifference Both must be taken into consideration if the infant's dermatitis is to be successfully treated

The adult patient with atopic dermatitis presents this dual problem within himself The physician must be concerned not

only with the dermatitis but with the patient's reaction to his disease. Frequently the management of the latter is the more difficult of the two. Many of these patients present themselves to the physician in a mental state of desperation, hopelessness, or utter confusion. They bitterly complain of the severe pruritus, which is frequently out of proportion to the visible dermatitis. They are notorious for their lack of confidence in their physician and are prone to challenge his therapeutic efforts unless immediate favorable results occur. They eagerly seize upon each new therapeutic suggestion, only to turn upon it and its suggester with an equal vigor. Many patients present an attitude of daring the physician to cure the dermatitis, and most patients take considerable pride in the fact that they have seen the best physicians in the vicinity. The physician himself frequently contributes to the patient's state of mind by allowing an attitude of hopelessness, indifference, or lack of confidence to become evident.

At present there is no specific cure for atopic dermatitis. Nevertheless therapeutic procedures are available which, if properly and confidently applied, will afford partial and at times complete relief to the majority of patients. These procedures are considered in the following paragraphs.

SYSTEMIC MANAGEMENT

Patients with atopic dermatitis are as a rule in good physical condition. Numerous studies designed to reveal abnormal functioning in various body systems for the most part have been nonproductive. However, certain abnormal reactions have been noted, including the patient's to stress situations [3] as measured by the Thorn test and the cold pressor test, and white dermographism, abnormal vasoconstriction of the peripheral blood vessels [4], abnormal response to heat, and a delayed blanching phenomenon of vasoconstriction to the injection of acetylcholine [5]. While many of these abnormalities have been elucidated through recent research, they provide a firm physiological foundation to previous empirical therapeutic measures such as avoidance of excessive heat, emotional stresses, fatigue and secondary infection.

Countless remedies during the years have been advocated for the treatment of this disease. Some of these now in use are intravenous calcium gluconate, crude liver extract, vitamin preparations, bacterial vaccines, antihistamines, and autohemotherapy These remedies have been referred to as supportive treatment, and certainly at times they seem to have beneficial effects. However *there is no evidence that any is specific, and probably their* initial value is related to the enthusiasm of the investigator and the psychological effect on the patient.

There are literally hundreds of therapeutic regimens which have been recommended for atopic dermatitis. It hardly seems worthwhile even to mention these by name, since none is in any way specific and, as a matter of fact, most are valueless. To perpetuate them in a review such as this would only lead to further confusion. As mentioned above, however there are several approaches which seem to have a bearing on trigger factors and which therefore deserve further consideration, some of them in detail.

Antibiotics. The antibiotics have added considerably to the management of atopic dermatitis. Their use is indicated whenever a local or systemic bacterial infection is present In addition, many patients in whom cutaneous bacterial activity is not particularly evident will nevertheless respond sometimes dramatically to adequate parenteral antibiotic therapy In some instances where a bacterial factor is strongly suspected and initial *antibiotic therapy has been ineffectual, culture for the organism* and sensitivity tests to the various antibiotics may indicate a need for a change to a more effective drug. Cultures and sensitivity studies are revealing an increasing number of strains of bacteria resistant to one or more of the commonly employed antibiotics and are accordingly of increasing importance for the proper control of damage produced by bacteria

Tranquilizers. Since it is well known that stress situations do tend to precipitate atopic dermatitis in many individuals it follows that drugs intended to modify or prevent emotional stress may be of value Perhaps the most favored remedy of this type has been phenobarbital a quarter to a half grain three or four

times a day This drug has been used for many years, primarily for its sedative action, and has ardent advocates, although a question may bo raised as to its over-all value. As a matter of fact, in some instances it would seem not only to be of no value but to be contraindicated, since the drug may counteract the patient s ability to resist the impulse to scratch and by this means lead to rather severe episodes of uncontrolled scratching.

More recently a large number of drugs with so-called tranquilizer properties have become available and are variously re ported to create a sense of well-being, to relieve anxiety to have a soothing effect on the central nervous system, to have antispasmodic, antihistaminic, antiserotonic, adrenolytic effects and a wide variety of other actions. Because of the increasing number and variety of these agents, the physician would do well to employ those tranquilizers with which he has had experience, including a detailed knowledge of their undesirable side effects and reactions. As might be expected, complications range from mild to severe and include a wide variety of undesirable side effects such as skin reactions, hypertensive effects, leukopenia, agranulocytosis, jaundice, and psychological abnormalities. The authors have had detailed and controlled experience with several of the tranquilizers, particularly meprobamate and reserpine [6, 7] It is the authors opinion that they are of some value in some patients, particularly for the control of emotional stress and anxiety which go hand in-hand with the eruption. Possibly their effect was best described by the wag who stated "Tranquilizers don t cure atopic dermatitis but the patients no longer give a damn.

In general, and considering the tranquilizers as a group it is well to keep in mind that they ha e been employed in one form or another for many years and too much must not be expected from their use

Steroids. The introduction of corticosteroids in the management of atopic dermatitis has proved to be of real importance These drugs, along with ACTH ha e been under investigation in atopic dermatitis for a period now of approximately seven years and their usage and dosage have been well defined. Most physi-

cians are now cognizant of the limitations and side effects of the steroids and are careful in their selection of patients for this type of treatment, taking such steps as are available to prevent complications.

Originally cortisone was the drug used in atopic dermatitis. Later it was replaced by hydrocortisone. These two drugs are effective therapeutic agents and will control the skin eruption in practically every patient if given in sufficient dosage. However the side effects of these two drugs are serious and include the development of varying degrees of Cushing's syndrome psychosis diabetes, episodes of sodium retention and serum potassium depletion, duodenal ulcers, demineralization of bones, and impaired ability to combat infection. Several years ago prednisone and prednisolone were introduced on the basis that the ratio of their antiinflammatory action to their other side reactions was much greater These are now used almost exclusively in the treatment of atopic dermatitis.

More recently two new promising steroids have been introduced, 6-methyl prednisolone and triamcinolone, on the basis that they possess a greater margin of safety Although they are more effective milligram for milligram, further more detailed and prolonged studies will be necessary to evaluate their relative degree of safety

In therapeutic doses all these have been found in our experience to produce undesirable side effects, and therefore it is necessary that proper measures be taken to minimize their incidence It is particularly important that patients with atopic dermatitis who are receiving these steroids be given an anti ulcer diet and antacids between meals and at bedtime, as the development of a peptic ulcer is one of the more common serious side reactions which we have encountered in this group of patients

It is our opinion that steroid therapy should be instituted in those patients with generalized and severe atopic dermatitis when all other modes of therapy have failed to give substantial relief [8] While we have encountered most of the side effects produced by steroid therapy it is again emphasized that the majority can be prevented by suitable management It is interesting that in the

large series of cases of atopic dermatitis which we have treated during the past 7 years the incidence of serious side effects has been minimal when contrasted to those patients receiving steroids for more serious diseases such as systemic lupus erythematosus and pemphigus. In this latter group, perhaps because of the high dosage required for control of the pemphigus and because of the increased age and poor nutritional status of the patients, the side effects associated with steroid therapy have been much more serious and have included osteoporosis, pathological fractures, perforated ulcers, development of diabetes, psychoses, and severe and fatal infections.

It cannot now be doubted that the corticosteroids are the most important contribution to the management of atopic dermatitis to date. However it is felt that the selection of patients for treatment with steroids is of prime importance, and those patients with only mild to moderate involvement should be controlled by other means. The dosage should be just sufficient to control the symptoms, and it is our feeling that it should be given in the manner recently outlined by Forsham [9] He has pointed out that normally the human adrenal cortex operates in a cyclic fashion, producing about 70 per cent of its total daily output from 2 A.M. to 6 A.M. It was his suggestion that maintenance dosages should be attempted in all but the most acute and life-endangering conditions from the bottom up At first one should attempt to give up to 30 mg of hydrocortisone or its equivalent at 9 A.M., thus circumventing the inhibition of the pituitary ACTH production during the crucial night period and thereby making the drug additive. If not successful, the drug should be given every 6 hours.

Dietotherapy In infantile eczema dietotherapy is ordinarily not particularly useful, but one does occasionally encounter spectacular results. Substitution of milk of another mammalian species is sometimes tried, and soybean- and meat based formulas are now in vogue In the case of the breast-fed infant some investigators have recommended that the mother eliminate the main offenders from her diet on the postulation that unchanged or only partially denatured proteins may pass into her milk. This pro-

cedure may be of some help, but probably through giving the mother a sense of active participation in the treatment at little cost in personal deprivation. Perhaps one of the best recent surveys of this subject is that of Hill, in which he states that "most of the time skillful local treatment does more good for infantile atopic dermatitis than anything else" [10] He goes on to point out that, while milk-free diets are sometimes of value they are being used altogether too much for every sort of skin eruption

In general it may be said that dietotherapy in children and adults has proved of limited value For years Rowe's elimination diets enjoyed considerable popularity and were thought by many to be worthwhile However where carefully controlled experiments were carried out it was not easy to ascribe any particular value to these diets for atopic dermatitis. Others have tried numerous elimination and "odd ball" diets, none of which seems to have any particular indication or merit. We are in agreement with a recent statement by O'Leary [11] that "rigid diets, often inadequate from the dietary standpoint and ineffectual against atopy should be avoided.

Since Hansen's demonstration in 1933 that infants with atopic eczema have low serum levels of unsaturated fatty acids, many favorable and unfavorable reports on the oral and local administration of these substances have appeared in the literature. A recent controlled study by Pettit led him to the conclusion that this type of treatment is "in no way preferable to the established methods of therapy" and it would seem that there is now available sufficient evidence to justify its abandonment

Glaser and coworkers in a series of articles [12 15] have recently presented the results of their studies of the prophylaxis of allergic disease in infancy and childhood If their interesting work is confirmed, it may prove to be of great value These authors presented a method of feeding the newborn human infant which significantly reduced the incidence of allergic disease not only during the newborn period but also in late childhood

Psychotherapy The literature is replete with studies of the psychological and psychiatric factors involved in atopic derma-

titis. Opinions as to the importance of these factors vary from none to all, and there is a considerable degree of conflict even among those best qualified to judge. Psychiatric treatment has gone all the way from superficial or mild nondirective therapy given by the amateur or inexperienced to complete psychoanalysis by the experts, with all gradations in between. Group psychotherapy has been reported favorably by some investigators as has superficial office psychotherapy. The results of all these methods have been very spotty and unsatisfactory. On sound medical grounds psychotherapy should be the treatment of choice if psychiatric factors are of much importance, but it should be recognized that in the hands of the inexperienced these measures are not without risk. In our opinion it is most important that the physician present an encouraging and sympathetic attitude toward the patient and permit ample time during office visits for him to discuss any problems he may wish to bring up, whether personal or medical. Those patients with psychiatric problems should be managed in cooperation with the psychiatrist. The psychiatric aspects of dermatologic disease are considered in greater detail elsewhere in this symposium.

Allergy Management. Hypersensitivity is a conspicuous characteristic of individuals with atopic dermatitis. The majority of patients upon skin testing reveal numerous sensitivities, particularly to common environmental antigens. Most prominent are local pollens, wool, silk, house dust, and feathers. The sensitivities vary in degree from time to time, and upon changes of environment new allergic patterns may develop. Experience has been disappointing with regard to the elimination from the diet and environment of materials giving positive reactions to skin tests. Desensitization procedures based on skin testing have been abandoned by many experienced physicians because of consistently poor results.

Change of Environment. An important adjuvant in the management of this disease is change of environment. It has been noted and verified that many individuals with atopic dermatitis do extremely well on hospitalization irrespective of the type of treatment used. In our opinion severe cases in either infants or

adults should be hospitalized until the dermatitis has moderated. Special care should be used with infants, since they are unduly susceptible to respiratory infections. In addition, many patients will improve by a change of environment to some other section of the country. While it is customary to refer patients to areas noted for moderate climates and a low humidity, the incidence and severity of atopic dermatitis in California seems to be similar to that found in other parts of the country. Furthermore, change of environment for patients residing in California is as effective as for those residing in New York. This implies that change of environment mediates its effect by psychological or allergic mechanisms as much as by climate. Sulzberger [16] on the other hand, feels that the most beneficial changes ensue as the result of the relief of the sweat retention syndrome which occurs so often in these patients.

LOCAL TREATMENT

The local management of atopic dermatitis is certainly the main prop of treatment of any case and is deserving of serious study and thought on an individualistic basis. Literally thousands of remedies of one sort or another have been advocated for application to the skin, and yet all these are entirely empirical, many of them have no purpose, and some are actually harmful. Overtreatment syndromes in the patient with atopic dermatitis are frequently encountered, and the authors would like to stress the desirability of simplicity in local therapy. It is necessary to study each patient individually and to approach each case with a consideration of the principles of therapy and the goal which one hopes to attain. The main considerations in this respect are

1. To allay itching to whatever extent possible. This will be considered in detail later.

2. Trauma to the skin should certainly be avoided, including trauma from wool, external irritants, soaps, detergents, and paints.

3. Most patients with atopic dermatitis have an accompanying ichthyosis which should receive special attention.

4. The recognition of the sweat retention syndrome in these

people is important, and steps should be taken not only to treat it when present but to prevent its development.

5. The local treatment is primarily intended to allay inflam mation, which in the acute case requires compresses and soothing lotions in the subacute, combinations of compresses and oily lotions or soothing ointments and in the chronic case, stimulating ointments.

6. The bacterial element has been mentioned before, but it is frequently very prominent and may require the use of systemically administered antibiotics along with one of the antibiotic ointments. It seems fairly well established that the choice here is neomycin with the addition of such antibiotics as bacitracin and polymixin B in order to broaden its activity Also if evidence of infection is present and the antibiotic ointment does not seem to be effective a culture of the organism and sensitivity studies are indicated. As a note of caution Neomycin may rarely induce sensitivity and in such circumstances other antibiotics such as Chloromycetin, erythromycin, or one of the tetracycline group may be substituted for local use.

7 Careful exposures to ultraviolet radiation and sun seem to be of value in the average case.

8. While roentgen ray was used quite commonly in the past for the treatment of this condition, the chronicity of the disease and the inability of such therapy to cure, together with the avail ability of more effective agents, makes the use of this modality of therapy less frequently necessary

Topical Steroid and Antibiotic Therapy The greatest single advance in local therapy is the use of steroids, either alone or in combination with antibiotics. These preparations are extremely effective in most cases and may be used with little fear of complications. There is some evidence that the fluorohydrocortisones may be absorbed in certain instances in sufficient quantity to cause a rapid gain in weight on the basis of sodium retention. However this is certainly an unusual complication and one which is rarely encountered. At the present time the most commonly used preparations contain hydrocortisone in the strength of 0.5

to 2.5% either in ointment or lotion form, with or without the addition of one or more antibiotics. Newer preparations include ointments and lotions of prednisone and prednisolone. They all seem to be equally effective but it does seem important to choose between the ointment or lotion base according to the relative state of inflammation of the skin.

TREATMENT OF PRURITUS

The pruritus which accompanies atopic dermatitis is undoubtedly the most difficult of all the symptoms to manage. It can be almost excruciating in some patients to the point where at times they become hysterical and excoriate their skin in an unbelievable fashion. In many patients it is paroxysmal and occurs in waves of almost unbearable agony.

In a recent review of this subject Lobitz [17] has considered the main factors contributing to intense pruritus as being trauma, inflammation, dryness, lichenification, the sweat retention syndrome and the release of H substance as a result of the trauma of scratching. Any one of or all these factors may be present in a patient with atopic dermatitis.

It is obvious then that the basic therapeutic aims must be directed toward correction of these factors to whatever extent possible. This includes antiinflammatory drugs such as the steroid antibiotic combinations, proper care of the skin to avoid trauma and chapping, and the avoidance of detergents, solvents, and drying lotions. In addition, hydration baths followed by a hydrophobic grease are worthy of trial. The avoidance of or recognition and treatment of the sweat retention syndrome is particularly important in the individual with atopic dermatitis.

One must also consider the treatment of pruritus in terms of both local and systemic drugs. The local management of pruritus was very unsatisfactory until the advent of hydrocortisone and related steroids. Many other drugs are used for this purpose, most of them being local anesthetics, but we believe their use should be abandoned. These drugs may produce some feeling of relief or comfort, but they all have a high capacity for producing dermatitis, and the majority are of little value. This is particularly

true in the case of the caine group of drugs and the antihistamines, and sensitization to these remedies is quite common.

The internal management of pruritus is also unsatisfactory Patients are prone to put great pressure on the physician for immediate relief, but for well-known reasons narcotics are contraindicated in addition to being habit forming some may directly enhance pruritus. In some patients moderate doses of phenobarbital or other tranquilizers may have some value for this purpose.

We wish to emphasize that the steroids in adequate dosage are the most effective single agent for the relief of pruritus accompanying atopic dermatitis and should be instituted in severe cases unless medical complications are present.

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Paul LeVan **17**

PRURITUS

Perhaps no single subjective symptom encountered in the practice of medicine can be so readily produced by such a variety of agents, direct and indirect, nor pose such a perplexing problem in causal determination and management for both the physician and patient, as that of the sensation of itching.

Pruritus is not in itself no matter how predominant or severe, a disease entity but rather represents a symptom which reflects a physiologic or pathologic state. Physiologic itching is produced by minimal excitation of the epiderm encountered in normal daily activities, for example, by changes in temperature, pressure, or even the observation of another individual engaged in scratching. Frequently the stimuli encountered are subconscious, and the resultant scratch reflex likewise does not enter the conscious sphere. On the other hand, pathologic itching is the result of a morbid process and reaches such intensity as to become distinctly unpleasurable and disturbing to the subjected individual.

It must be appreciated in clinical evaluation that extreme variation in the itching threshold exists in different patients. It is common experience to see one patient with a usually pruritic dermatosis complain little of itching, while, on the other hand, an isolated plaque of erythematous epiderm renders another patient sleepless distraught, and a distinct challenge to the practitioner

While these variations may have a yet unknown basic *raison d'être* it is probable that differences in peripheral and/or essential nerve thresholds of response are paramount in the production of the varying subjective clinical phenomena. A similar pattern is recognized in the differing response to pain stimuli as well as to tickling in different individuals. Generally itching or ticklish sensations do not occur in areas of hyperalgesia but are intensified in areas of hypoalgesia. Similarly pain perception occurs more readily in itching skin than in nonitching skin. Sharp pain heat, cold, or trauma occurring in an area of itching will abolish the latter sensation.

Inasmuch as the peripheral nerves carrying the sensation of itching transmit these impulses to the posterior roots of the spinal cord and thence up the spinothalamic tracts to the thalamus and cortex, stimulation of these higher nerve centers may increase the sensation of itching. On the other hand, the depression or sedation of these areas may decrease or abolish itching.

While the central nervous system of human beings plays an important role in the recognition, subjective intensity of and modification of response to, the itching stimulus, the initiation of this symptom by and in the central nervous system per se is regarded as relatively rare. Nevertheless, certain pathologic states of the brain as discussed below under psychoneural factors of itching are associated with pruritus, and experimental animal studies likewise have demonstrated the existence of a purely central type of itching.

Pruritus is generally made up of two components pricking itch and burning itch. The first is thought to be transmitted by the myelinated nerve fibers and the second by unmyelinated fibers. This is analogous to the localized discrete primary fast pain and the diffuse secondary or slow pain carried respectively by these same nerve fibers. The primary or pricking, itch is spontaneous, short lived and occurs in normal itch spots in all normal persons, or can be produced by many disease processes such as inflammatory dermatoses, heat, histamine and insect bites. The secondary type, *burning itch is encountered in* itchy skin and is of long duration, surrounds an area of primary or spon-

taneous itching, and is quite diffuse. Such sensory stimuli as pressure, temperature change or light touch can initiate secondary itching. The sensation of being ticklish is in part a form of "itchy skin.

MECHANISMS OF PRODUCTION AND RESPONSES

A review of studies of the mechanisms producing pruritus indicates that any stimulus of low intensity can produce itching. An intensification of these stimuli ultimately produces pain. Further investigation has shown that the proteolytic enzymes (proteinases) functioning within a physiologic pH environment can produce pruritus. These substances are believed to have a pathogenetic effect in a varying degree upon the sensory pain receptors. The transition of the sensation of itching to that of pain becomes dependent upon the degree or intensity of the deleterious effect of these proteinases upon nerve endings or perhaps upon the variation of threshold response of the end organs to noxious stimuli. It becomes apparent to the clinician that the variety of initial internal and external stimuli that result in pruritus probably act through one or a group of physiochemical mechanisms inherently related to epidermal physiology itself. The release of epidermal proteinases by a variety of stimuli seems to be for the present the most likely *modus operandi* in the mechanism of the production of pruritus.

The oft-sought for and frequently lacking objective signs of skin changes in relation to pruritus have led to a popular and often erroneous conclusion that the itching at hand is psychogenic in origin. It has been aptly demonstrated that the superficial presence of proteinase in the epidermis may be accompanied by severe pruritus although erythema, edema, or urtication are conspicuous by their absence. Similarly the hypersensitive state, with or without circulating antigens, may alone be responsible for intense pruritus totally unaccompanied by any visible cutaneous pathologic change.

The extension of pruritus from an original site to an adjacent, or indeed to a generalized area is a commonly observed phenomenon. It is analogous to the spread of skin hyperalgesia from

the site of original trauma and injury to a large surrounding area. The slightest stimulus, however unproductive in "normal" skin, is capable of setting off a reaction of the most intense pain or pruritus in these sensitized adjacent areas

Temperature Temperature has long been known to have a marked effect on the skin's itching threshold. The lowering of skin temperature by climatic conditions, cold compresses, absence of clothing or bedcovering, or evaporants such as menthol and camphor frequently will temporarily relieve pruritus. On the other hand heat applied in any form, or vasodilitation, no matter how produced, will usually result in increased itching. These peripherally induced conditions are not alone in their effects upon pruritus, for centrally acting medications likewise may exert a profound influence For example a mild analgesic such as aspirin may at times afford considerable relief while an opiate such as morphine may operate conversely

While the subject's response to itching often results in a pleasurable sensation sometimes simulating sexual satisfaction, it is just as frequent to have the itch sensation replaced by an induced painful stimulus. Such traumatic practices as pressing, digging, pinching, rubbing, stroking, and particularly scratching are all enlisted in various circumstances to terminate the itch sensation The resultant injury to the skin and subsequent reparative processes have become recognized and identified with the itch-scratch cycle.

Trauma. Scratching or other similar traumatic aforementioned practices eventually serve to intensify and prolong the itch sensation through several mechanisms. They alleviate the immediate pruritus by replacing the monotonous low intensity stimuli causing itching with a mild to severe pain sensation. In the production of pain, epidermal structures must undergo traumatic injury which in turn is followed by regenerative and reparative responses. There results a thickening of the stratum corneum and underlying epiderm manifesting itself in lichenification or accentuation of the normal skin lines. Scratching (or pain production) is rarely if ever confined to the locus of primary itching but rather is carried over well into and frequently beyond, the

surrounding area of itchy skin. This peripheral zone in turn becomes more intensely pruritic with an accompanying spreading out of the zone of itchy skin. Thus, a pattern simulating the visibly extending concentric waves produced by a pebble dropped into still water is recognizable in the gradual expansion of the primary itch area to a large diffuse plaque of itch-scratch epidermis. The superficial tissues in such an area have undergone hyperkeratinization resulting in increased dryness and blockage of sweat pores, both factors producing a greater tendency toward initiation of the itch sensation.

When the trauma of scratching is great enough to denude the epidermis and its pain receptors, itching ceases. However as the excoriation is repaired, pain receptors return, and the itching sensation may then be produced by the same mechanism as the healing of a cut finger or a surgical wound.

Trauma can play a further role in the subsequent production of itching by effecting the release of histamine from mast cells. The presence of histamine or histamine-like substances followed by the triple response of Lewis is a well-recognized mechanism in the production of itching accompanied by urtication.

CAUSATIVE FACTORS

The production of pruritus, as has been previously noted, can be brought about directly or indirectly by a variety of morbid states. For the sake of discussion, these may be classified as (1) physiologic (exaggerated to the pathologic state) (2) externally produced, (3) internally produced (4) psychogenic.

Physiologic. Physiologic pruritus is unaccompanied by visible skin change and is regarded, for the most part, as subconsciously existent. However any thought, sight, or sound accentuating this subconscious stimulus may result in a conscious level of itching and a reflex scratch response. The patient who first experiences itching when restricted in his activities or confined to his bed, as well as the individual who, busy all day is unaware of itching and at night experiences unbearable paroxysms of this sensation, are examples in point of the shift from the subconscious to the conscious levels. When such transition occurs from the subcon-

scious physiologic state to the conscious pattern, with or without morbid neurocutaneous alteration, then a pathologic pruritic condition exists.

Externally Produced. Externally produced pruritus embraces a wide variety of frequently encountered agents. They share in common—whether through primary irritancy allergic reaction, temperature and moisture alteration, or some other basic physiologic disturbance—the production of physical insult to the epidermis. The intensity of injury as well as the degree of epidermal and central response govern the level of pruritus produced.

Among the more commonly encountered external factors of cutaneous diseases producing itching are those listed below

- I Contactants
  - *A* Chemical
    - 1. Primary irritants
    - 2. Allergens
  - *B* Mechanical
    - 1 Clothing
    - 2. Traumatic
  - *C* Thermal
  - *D* Moisture ±
  - *E* Solar
- II. Cutaneous diseases
  - *A* Urticaria
  - *B* Seborrheic dermatitis
  - *C* Dermatitis herpetiformis
  - *D* Lichen planus
  - *E* Pityriasis rosea
- III Infections
  - *A* Bacterial
  - *B* Fungal
  - *C* Viral
  - *D* Generalized neurodermatitis
  - *E* Atopic dermatitis
  - *F* Lichen simplex chronicus
  - *G* Senile dry skin
  - *H* Localized pruritus (anal, vulvar scrotal)
- IV Infestations
  - *A* Pediculosis, scabies
  - *B* Pinworm
  - *C* Insect bites

Internally Produced. As varied as the external factors in itching are those of endogenous origin. The exact mechanism of production of pruritus in this group is likewise obscure in many instances. Those states more commonly associated with the endogenous production of itching are

Drug sensitivity	Liver disease
Lymphoblastomas	Renal disease
Diabetes mellitus	Neoplasms
Pregnancy	Psychoneurogenic disturbances

Pruritus due to the ingestion of drugs may or may not be accompanied by primary cutaneous lesions. Among the more common drugs producing pruritic reactions with primary cutaneous lesions are the antibiotics, barbiturates, phenolphthalein, the antimalarials, Thorazine, halogens, and heavy metals. Pruritus unaccompanied by primary skin lesions but frequently associated with secondary changes due to scratching, rubbing, and excoriation is most often related to such drugs as the opiates, arsenicals, and the antibiotics.

Lymphoblastomas, such as Hodgkin's disease, lymphosarcoma, and leukemia, are particularly characterized by their associated intense often paroxysmal pruritus, which may appear long before the lymphoma becomes clinically recognizable. The itching may be accompanied by or be independent of cutaneous morbid manifestations. While radiation or chemotherapy may temporarily alleviate the pruritus, it is not uncommon to observe a temporary increase in itching or the onset of erythema multiforme and/or urticaria following destruction of the neoplastic tissue by treatment

The mechanism of the production of pruritus in diabetes remains obscure It is usually generalized, unaccompanied by visible cutaneous lesions, and ceases when the diabetes is brought under control. Indeed, many patients and physicians recognize pruritus as a warning signal of an uncontrolled diabetic state.

Pruritus during pregnancy represents numerous clinical syndromes varying from generalized pruritus, anogenital pruritus, and pruritus of the mammae to localized itching in the areas of striae Herpes gestationis, a severely pruritic dermatosis, has

shown good response to measures aimed at raising the progesterone level. Similarly other types of pruritus encountered in pregnancy have been found to respond to progesterone level increases.

Hepatic damage whether accompanied by jaundice or not, is frequently associated with cutaneous pruritus. It is more commonly found in obstructive liver disease than in parenchymatous involvement. While the mechanism remains unknown, the presence of bile pigment in the skin is not always accompanied by pruritus, as evidenced by its only occasional occurrence in hemolytic anemia with jaundice. As liver function approaches a normal status, itching promptly disappears.

Pruritus associated with urinary tract pathology may be either metabolic such as that accompaning azotemia, or mechanical, as observed in prostatic or other obstruction to urinary flow not resulting in parenchymal damage or physiochemical disturbance. The surgical or mechanical relief of such obstructed flow is often promptly followed by cessation of itching.

Carcinomatous and sarcomatous neoplastic diseases present pruritus with sufficient frequency to indicate thorough investigation for the existence of these diseases in those patients with persisting pruritus of undetermined cause. As in lymphoblastomas, destruction of tumor cells either through treatment or spontaneous dissolution not infrequently results in severe pruritus. This is attributed to either absorption of toxic products or the release of antigenic substances from the degenerating tissue cells.

Psychoneural. The range of psychoneural disturbances resulting in pruritus as a prominent symptom is extensive and varied. From the psychosomatically induced or aggravated pruritic state of neurodermatitis, urticaria, angioneurotic edema, trichotillomania, atopic dermatitis, neurotic excoriations, and dermatitis factitia to the pruritus of tabes dementia paralytica, manic depressive psychosis, epilepsy and delusions of parasitosis, a varying degree of central nervous system aberration is pathogenetically involved. This group of cutaneous pruritic manifestations pose the most difficult problems in their management. The determination, evaluation, and removal of the underlying mental

disturbances often defy the most expert and experienced of psychiatrically trained personnel. This is borne out by the frequency of failure of the psychiatric approach in relieving many of these patients.

It must be kept in mind that localized pruritus may serve as an outlet for some psychological maladjustment and that removal of this psychocutaneous reaction pattern may precipitate a far more significant and serious psychiatric disturbance. This is analogous to the patient whose complaints are referable to the gastrointestinal tract, cephalomalalgia, muscular aches, or neuro-allergic responses, wherein the removal of the outlet site often invites more disastrous sequelae. It has frequently been stated that the patient who scratches, with or without cutaneous changes, seldom commits suicide. Perhaps this mechanism is in reality a barrier against self-destruction.

The frequency of occurrence of the psyche-induced pruritic dermatoses in certain types of individuals has evolved a pattern of patient often instinctively recognized by the dermatologist. They are doers, not dreamers; anxious, not complacent, tense, not relaxed, frustrated, not satisfied, and often bombastic, rather than retiring. Their threshold of cutaneous sensitivity is intermittently lowered with resultant central perception of, and response to, otherwise ignored pruritic stimuli. This is demonstrated by the fact that pruritus is absent while such individuals are absorbed in meeting a challenge of one sort or another but they will, upon deviating from the project at hand, expend their energies pathogenetically in the itch-scratch cycle.

THERAPY

Before considering the special management of certain clinical symptoms characterized predominately by pruritus, it would be well to review the basic concepts of the management of pruritus per se. In general, treatment may be divided into two broad categories: (1) the determination and removal of the cause and (2) symptomatic relief through the use of external and internal agents.

Determination of Cause

While the determination and removal of the cause is the most direct and effective approach to the problem, it frequently proves to be a task beyond our capabilities. Such factors as an initial pruritus caused by a specific agent being subsequently maintained and intensified by secondary responses, such as trauma and psychological aberration, render satisfactory management a most complex problem. Further, the exact mechanism of the production of pruritus remains undetermined in a large percentage of patients with pruritus, so that a physiologic approach in management is all too often unavailable. There remains then a major reliance upon empiric, indirect, and direct methods which are known to give symptomatic relief. These may be divided into psychological, topical, and systemic therapeutic categories.

Symptomatic Relief

Psychological. The psychological approach to management as presented here does not include expert psychiatric evaluation and therapy in the usual sense, but rather the establishment of rapport between patient and doctor. If the determination and removal of the specific cause has been found unobtainable and other measures must be utilized, this rapport becomes a prime factor in therapy. Sympathetic understanding, encouragement of the patient to "get it off his chest," accompanied by a detailed explanation of the problems involved, further coupled with a firm demand for execution of prescribed therapeutic procedures, often render the patient an effective colleague rather than a frantic adversary. Instillation of confidence by the above approach is a desirable and necessary adjunct of treatment.

Topical. Topical treatment does not embrace merely what we "put on," but also what we "take off" the involved epidermis. Removal of external contributing or aggravating factors such as trauma, irritating and or sensitizing preparations, temperature and moisture control, eradication of parasitic infestation, and elimination of bacterial and mycotic infection are all examples of the "taking off" of contributing or aggravating factors. This ac-

complishment, when clinically indicated, is a prime function in satisfactory management. However it cannot always be obtained without the substitution of one type of inciting factor for another For example, an antipruritic lotion may temporarily relieve the itching, but a contact dermatitis may supervene, and the pruritic complex may be heightened rather than diminished. To help meet such contingencies, it is well to bear in mind that inflammation per se, regardless of cause, is most frequently involved in the dynamics of pruritus. Hence, consideration of antiinflammatory topical measures appears in order These topical measures must be nonirritative, nonsensitizing, free of toxicity readily available to apply and easily removed, not unpleasant aesthetically to the patient, and, above all, prompt in their relief of pruritus. When judged by the above criteria, such topical agents as the caine products and antihistamines are found wanting, not only because of their inconsistent efficacy but primarily because of their relatively high sensitizing potentials. Both these types of topical antipruritics are deemed contraindicated in the management of pruritus.

Compresses, tepid, cool, or ice cold, comprise one of the most effective quick-acting agents for relief of paroxysms of pruritus. It appears that the chemical type of compress is not as important a factor as its prompt application at a tepid to cold temperature comforting to the patient Boric acid (1 level tablespoonful per quart) skimmed milk, followed by thorough rinsing, 1 20 Burow s solution, colloid solutions, diluted witch hazel, diluted alibour water and 1% sil er nitrate solution as compressing agents all have their advocates but in practice offer little advantage one over the other Excessive hot compresses of any type however are contraindicated, for although temporary relief is afforded the patient, the sequelae of vascular dilatation and engorgement of tissues with subsequent increased pruritus far outweigh the temporary relief obtained. Avoidance of tissue maceration through the excessive use of wet dressings is paramount for such damaged skin or mucous membranes are incapable of repair and offer little resistance to trauma or bacterial and mycotic invasion. Colloid, tar and other medicinal baths may be regarded in a sense as

generalized compresses, for although the cooling effect of evaporation of localized compresses is not attained, the temperature control and residual coating of the epidermis with therapeutic agents is similar to that of local compressing. In addition, the relaxing, soporific effects of prolonged hydrotherapy are valuable adjuncts in preparing the patient for a good night's sleep.

Liniments and lotions containing such agents as zinc oxide talc, starch, glycerin, and olive oil, to which are added such antipruritics as phenol 1%, camphor 0.5%, menthol 0.25%, or liquor carbonis detergens 5 to 10% are of value as antiinflammatory and antipruritic agents. In addition to the cooling effect of lotion evaporation and the antipruritic properties of the added ingredients, there is also the mechanical coating of the hypersensitive inflamed tissues. However, excessive accumulation of dried lotion, particularly in intertriginous areas, may lead to persistent trauma with resultant folliculitis and abrasion. Where feasible lotions should be soaked off for the most part, without traumatic removal, before succeeding applications are made. Prolonged use of liquor carbonis detergens or other tar derivatives should be avoided in intertriginous and hairy areas because of the frequent production of folliculitis. Steroid-containing lotions will be discussed below in conjunction with other steroid topical agents.

In addition to lotions, the application of alcoholic solutions of bacteriofungistatic dyes such as Castellani's paint and mild caustics such as 1% silver nitrate are of great value particularly in intertriginous areas. Care or abstinence must be exercised in instances of raw weeping surfaces because of intense subjective discomfort and possible primary irritation of the underlying process, but in subacute and chronic inflammatory cutaneous states such application of these dyes is of decided benefit.

Protective ointments and pastes are also utilized, often primarily for their mechanical coating, to reduce cutaneous stimuli. They are of particular benefit about the urethral and anal orifices where excretion may be significantly irritating and itch provoking. The removal of these protective coatings must be accomplished with the greatest of care to avoid trauma to the pruritic

tissues. Prior soaks with mineral oil often minimize the potential trauma of removal.

Specific antipruritic preparations such as Quotane, Tronothane hydrochloride, and Dyclone have been extensively studied and clinically used with satisfying results in 57 to 84 per cent of patients so treated. These topical antipruritics are not of the caine variety and the index of sensitization is relatively low for all three preparations. They are available in ointment, cream, and lotion form, the ointment or cream form being utilized in dry pruritic states and the lotion in weeping eczematous dermatoses.

The corticosteroids employed topically have, to date, been found the most effective antipruritic preparations available. While early cortisone-containing applications were singularly ineffective, the later derivatives such as hydrocortisone, fluorohydrocortisone, and Vioform hydrocortisone have proved to be outstandingly useful in topically controlling pruritus. They are available in both ointment and lotion form in strengths varying from 0.5 to 2.5% for the hydrocortisone preparations and 0.05 to 0.25% for the fluorinated steroid ointments and lotions. The combining of these steroids with such antibiotics as neomycin, polymyxin, and bacitracin has extended their usefulness to those dermatoses in which bacterial infection plays a role. For monilial dermatitis, Mycostatin may be combined with a steroid preparation with gratifying results.

It must be pointed out that use of steroid preparations in their highest (and most expensive) concentration is frequently not necessary to obtain symptomatic relief. A 1% hydrocortisone preparation or a 0.1% fluorinated compound will usually yield as much comfort as the stronger preparations available. While localized processes such as encountered in lichen simplex chronicus and pruritus ani or vulvae are particularly suited to steroid application, it is impractical to use these expensive preparations over larger areas of pruritic epidermis. Less costly topical agents such as Dyclone, Quotane, Nivea, or Lubriderm with phenol, camphor, and/or menthol will often suffice for more extensive areas.

Systemic. Systemic antipruritic therapy may be divided into sedative, antihistaminic, tranquilizing, and antiinflammatory (steroid) categories with varying combinations of these agents.

SEDATIVES. Sedatives such as barbiturates, bromides and chloral hydrate have long been used in the management of pruritis. While some benefit has been obtained by their administration, such undesirable effects as *uncontrolled nocturnal excoriation*, habit formation, "hang-over," development of tolerance and dermatitis medicamentosa have all too frequently been encountered. The use of the aforementioned drugs is not recommended in the management of pruritus, particularly in view of the quieting effects observed with the antihistaminic and tranquilizing compounds.

ANTIHISTAMINICS. The antihistaminics in addition to their specific neutralizing effect upon histamine, as discussed in the management of urticaria, exercise marked sedative and soporofic side effects. These may be so pronounced at times as to contraindicate their use in significant dosage in ambulatory patients. On the other hand, their judicious use to obtain sedation and sleep often accomplishes a major objective in the management of the pruritic patient. Dosage must be individualized for the problem at hand and can be regulated to meet the patient's needs for symptomatic relief while allowing him to remain usefully active. It is not important as to which of the clinically established antihistaminics are used, but rather that it be used wisely and effectively. A further discussion of the use of the antihistaminics will be found in the chapter dealing with the management of urticaria. *The principles there set forth are equally applicable in the treatment of pruritus.*

TRANQUILIZERS. The tranquilizers, or ataractic drugs, are another group of valuable therapeutic agents in the management of pruritus. As previously discussed, the psychologic and neurogenic factors in the production and maintenance of the pruritic state are of prime importance, and any agent capable of diminishing, if not abolishing, such factors, is valuable in management. The lessening of tension, emotional instability and antagonism are frequently observed effects of these drugs. In addition, improved

sleeping habits are usually obtained. Such undesirable side effects as depression, excessive drowsiness, and increasing tolerance are encountered but may be minimized by regulation of dosage and selection of drug. In our experience, meprobamate (e.g., Equanil, Miltown) and hydroxyzine (e.g., Atarax) are preferable for tranquilizing to the rauwolfia and chlorpromazine preparations. Many newer tranquilizing agents are rapidly becoming available and appear worthy of clinical trial. Again, as with the antihistaminic drugs dosage employed and the individual patient response are the prime factors to be considered, rather than which tranquilizer is used.

One of the newer preparations worthy of comment in the management of pruritus is a phenothiazine derivative marketed under the name of Temaril. In addition to exerting a pronounced tranquilizing and soporific effect and a moderate antihistaminic activity this drug has, to date, demonstrated in a wide variety of pruritic dermatoses the most antipruritic potential of all the antihistaminic and tranquilizing drugs the author has thus far studied. While it is not effective in all instances, the frequency of beneficial response (in 60 to 80% of patients) coupled with the low incidence of side reactions and inappreciable toxicity as reported to date make this drug one of choice in the management of the pruritic patient The usual dosage employed is 2.5 mg three times a day with meals, and 5 mg 1½ hours before bedtime. The product is available in tablet and liquid form. Temaril is particularly useful in conjunction with steroid therapy when the latter is used for controlling inflammatory pruritus, inasmuch as it allows for the reduction of the steroid dosage once the inflammation has abated while Temaril maintains an antipruritic effect. It is believed that the rebound phenomenon is much less frequently observed and is less intense when steroids are withdrawn and the patient maintained on an adequate dosage of Temaril

STEROIDS. The steroids, ACTH, or cortisone and its derivatives have been widely used in the pruritic dermatoses. Adequate dosage to alleviate inflammation should be employed in short courses rather than inadequate dosage over longer periods of time It should be borne in mind that beneficial effect has been

Systemic Systemic antipruritic therapy may be divided into sedative antihistaminic, tranquilizing, and antiinflammatory (steroid) categories with varying combinations of these agents.

SEDATIVES. Sedatives such as barbiturates, bromides, and chloral hydrate have long been used in the management of pruritis. While some benefit has been obtained by their administration, such undesirable effects as uncontrolled nocturnal excoriation, habit formation, "hang-over" development of tolerance and dermatitis medicamentosa have all too frequently been encountered. The use of the aforementioned drugs is not recommended in the management of pruritus, particularly in view of the quieting effects observed with the antihistaminic and tranquilizing compounds.

ANTIHISTAMINICS. The antihistaminics in addition to their specific neutralizing effect upon histamine as discussed in the management of urticaria exercise marked sedative and soporofic side effects. These may be so pronounced at times as to contraindicate their use in significant dosage in ambulatory patients. On the other hand, their judicious use to obtain sedation and sleep often accomplishes a major objective in the management of the pruritic patient. Dosage must be individualized for the problem at hand and can be regulated to meet the patient's needs for symptomatic relief while allowing him to remain usefully active. It is not important as to which of the clinically established antihistaminics are used but rather that it be used wisely and effectively. A further discussion of the use of the antihistaminics will be found in the chapter dealing with the management of urticaria. The principles there set forth are equally applicable in the treatment of pruritus.

TRANQUILIZERS. The tranquilizers or ataractic drugs, are another group of valuable therapeutic agents in the management of pruritus. As previously discussed, the psychologic and neurogenic factors in the production and maintenance of the pruritic state are of prime importance, and any agent capable of diminishing, if not abolishing, such factors, is valuable in management. The lessening of tension, emotional instability and antagonism are frequently observed effects of these drugs. In addition, improved

idiopathic instances of pruritus ani are essentially neurodermatitic in origin. The clinical picture here is usually of the dry lichenified, fissured type with occasional wet eczematous flare-ups occasioned by trauma or contact sensitization. Other areas such as the nuchal region of the neck, external ear canals, or circumscribed plaques on the extremities may concomitantly be involved in a lichen simplex chronicus response. These patients are often tense, anxious, perfectionistic, and present psychosomatic patterns involving various other systems.

Such general diseases as lymphomata, liver disease, diabetes, parasitic infestation, and allergic responses may become manifested as pruritus ani. Among the more common allergic responses are those induced by foods, deodorants, hygienic pads, antibiotics, and caine derivatives.

Almost irrespective of which causative factor or factors are present, pruritus ani may clinically vary from acute denuded, ulcerated, weeping dermatitis to dry lichenified, fissured, crusted, and intensely pruritic cutaneous involvement. Intermediate stages and combinations of the aforementioned signs and symptoms may often be seen in one individual. This is to be anticipated in the anal area where secondary factors such as trauma, bacterial or mycotic infections, contact sensitization, and maceration or sweat retention may all play a part in altering the initial pathologic changes.

While the task of determination and removal of the cause is being undertaken, it is essential that the patient be given symptomatic relief from his pruritus. Prompt institution of those topical and systemic measures previously outlined along with patient understandi g and sympathy will often convert the antagonistic, uncooperative individual to a model" patient. The early introduction of a substitute for the scratch response is desirable and may take the form of a cold compress, a tepid starch bath, or an antipruritic cooling lotion. A patient cannot be told, Don t dare to scratch, but must be schooled repeatedly in the dictum "Don't reach for your backside—reach for the cold wet cloth on the night table Repeated admonition and coaxing will frequently bring about the substitution reflex. Such cold wet dressings as boric

acid (1 tablespoonful to 1 quart) skimmed milk (rinsed off with water) or dilute 1 32 Burow s solution have been found effective in relieving the acute paroxysms of itching. These may be followed by the application of a lotion as suggested in the Appendix. Heat is not considered desirable for although temporary relief may be obtained it is believed that subsequent vascular engorgement and increased temperature may lead to further pruritus and sequelae Prolonged or too frequent wet dressings are likewise deemed inadvisable because maceration of tissue results in further delay in healing as well as increased susceptibility to secondary microbiologic infection

As soon as the subsidence of the acuity of the process permits, the daily application of Castellani's paint has been found to be of great value The bacteriacidal and fungicidal properties of this preparation, coupled with its astringent and drying effect have been found to accelerate healing Because of the alcohol vehicle this topical preparation cannot be used in the very acute exudative denuded, eczematous phases of pruritus ani However when once tolerated by the patient, symptomatic relief is increased and a protective coating is manifest following its use Another valuable topical preparation in the subacute and chronic phases of anal dermatitis is the application of Vioform hydrocortisone cream. The combination of a topical steroid with a bacteriofungicidal preparation has afforded many of the author s patients adequate relief In those instances where monilial infection, primary or secondary is manifested by the characteristic macerated or glazed, intensely erythematous, cutaneous reaction, the use of Mycostatin orally and locally is deemed of value

In addition to the above suggestions of topical therapy certain don'ts should be given to the patient. They may be listed as follows

1 Don t use soap and water on the affected area. Cleansing may be accomplished by compressing or a starch bath.

2 *Don't use toilet tissue for postdefecation cleansing* Absorbent cotton soaked with cool or tepid water or dilute boric acid solution should be routinely employed and gentle repeated cleansing continued until the cotton returns spotless. If desired,

a cleansing flannel, mildly medicated cloth is available on the market under the trade name of Tucks. The cloth is impregnated with a preparation of glycerin and Hamamelis water which affords a soothing, moist cleansing agent.

3. Do not apply caine or antihistaminic preparations regardless of any temporary relief obtained.

4. Do not scratch, but substitute the cold compress, manual pressure, a lotion, or prescribed ointment.

Among the ointments used, none should be employed in the acute weeping, eczematous phase. In the subacute or chronic stage, in addition to the fluorinated steroids with or without Vioform, antibacterial, mild antifungal, and protective preparations may be utilized. A low index of sensitization of all these preparations is a prime requisite, and any evidence of intolerance is a *sine qua non* for discontinuation and the substitution of another preparation. Protective ointments such as hydrated petrolatum, zinc oxide ointment, or Lassar's paste often stand in good stead in preventing fissuring, abrasion, and resultant discomfort.

It is reemphasized that in addition to the special measures here suggested for relief of distressing symptoms, systemic therapy as discussed under general management of the pruritic patient, should be utilized to the fullest extent.

X-ray therapy long a pillar in the treatment of pruritic dermatoses, is now deemed a measure of last resort in the treatment of pruritus ani. Furthermore, it is believed that the use of this modality without regard for causative factors, state of tissue damage, and unaccompanied by suitable topical and systemic therapy is merely a shotgun approach that can, at best, afford very temporary if any relief The present antagonistic attitude of the lay public to the use of x-radiation, coupled with the sharply limited allowable total dosages to this area, make this modality a tool for the most hard pressed and experienced therapeutist.

Further such surgical procedures as the undercutting operations, alcohol and anesthetic injections, and similar nerve pathway disrupting measures have not, in our opinion, stood the test of time. Recurrence is not infrequent, and resulting sequelae

may be of such proportion as to render these modalities of questionable value Among the undesirable sequelae may be mentioned paresthesias perianal and perirectal necrosis or suppuration, and incontinence Further our more recent understanding of tissue regeneration as set forth by Lobitz recognizes subsequent epidermal thickening, obstruction of sweat pores, formation of epithelial inclusion cysts, and foreign body granulomata as frequent occurrences following various degrees of trauma to the skin and subjacent tissues.

In summation of the treatment of pruritus ani, the following prime factors are reiterated classification of the type of involvement and its causative factors treatment of the stage of the dermatitis at hand the combined use of topical systemic, and psychologic modalities as indicated the institution of essential don'ts and the reservation of x-ray therapy and surgical or injection disruption of nerve pathways for the most experienced therapeutist.

Pruritus Vulvae Much of what has been stated in connection with the management of the pruritic patient and the patient with pruritus ani is applicable to the female afflicted with pruritus vulvae However there are special considerations in the management of this problem which are essential to successful results.

Causal determination has been previously set forth as a basic approach to any problem of pruritus. It is especially requisite in dealing with the pruritic vulva and often attainable through clinical and laboratory (including biopsy) evaluation. The aid of a gynecologist or dermatologist should readily be enlisted where necessary Causative factors may be divided into *local* and *systemic*, the former designating primary involvement of the vulva or any portion of the genital tract and the latter including those conditions not originating in, but reflected by involvement of the female genital area. Local conditions include trichomonas, monilial or bacterial, infection, and/or sensitization, contact dermatitis, trauma, intertrigo senile and atrophic changes, leukoplakia, leukokeratosis and kraurosis vulvae hypertrophic, lichenified changes, and malignant degeneration. The aforementioned contact dermatitis may arise from soaps, douches, deodorants,

vaginal insertions (for treatment or contraception) menstrual pads, shaving preparations, perfumed toiletries, and snug under clothing. Systemic conditions reflected in genital pathogenic response include diabetes, liver disease, allergy (particularly drug sensitivity) parasitic infestation various dermatoses such as seborrheic dermatitis, psoriasis lichen planus, viral infection, vitamin deficiency anemia, lymphoblastomas, and finally neurogenic disturbances. Unfortunately as in the causes of pruritus ani, this latter category comprises a significantly large component of those patients with pruritus vulvae.

In younger individuals (premenstrual) such factors as bacterial infection, pinworm infestation, trauma of masturbation, and gonorrheal vaginitis must be given special attention. In older patients (menopausal and postmenopausal) senile changes carcinoma, moniliasis diabetes, and vitamin deficiency are to be ruled out.

The same basic principles of local and systemic therapy as set forth in the treatment of pruritus per se and pruritus ani obtain here. In addition to nonirritating removal and treatment of underlying causative factors, topical and systemic therapy must be directed toward the immediate epidermal state at hand. Soothing bland compresses, sitz baths, lotions, and local and systemic steroids, if necessary must be utilized in the acute, weeping states with graduation to paints, creams, and ointments as the drying and tolerance of tissues permit. Local cryotherapy and x-ray administration should be left to the expert and are particularly of value in the hypertrophic, lichenified type of pruritus vulvae associated with lichen simplex chronicus or neurodermatitis. In the treatment of pruritus vulvae, particular attention must be directed towards the prevention of folliculitis in this hirsute area. Heavy ointments, tar products, and salicylic acid are not well tolerated about the vulva and should be used with discretion and only for short periods of time The periurethral and intralabial use of a protective paste such as Lassar's is of value in giving comfort to the acute ulcerated patient, but its application should be confined to the proper areas, avoiding the perivulvar hair

Much has been written advocating the use of topical and systemic estrogens particularly in the senile, atrophic types of

pruritus vulvae While the rationale of such therapy appears sound actual results are disappointing for the most part. In those instances where psychogenic disturbances due to menopause have been evident, improvement from systemic administration has been observed, but apparently more as a result of the over all psychoneurogenic response than because of a direct local affect Satisfactory topical use of the estrogens is confined to a small, select group of hormone-deficient vulvar entities of the postclimacteric group.

Surgical intervention as in the problem of pruritus ani should be reserved as a last resort and performed by the most expert and experienced The instance of vulvectomy followed by recurrence of identical original symptomatology has occurred with sufficient frequency to evoke hesitancy in the use of this radical procedure Injection techniques, likewise while frequently successful in expert hands, have been accompanied by such complications and sequelae as to render their use a reservation for the most experienced.

Inasmuch as a large proportion of pruritus vulvae is due to, or intensified by psychoneurogenic factors, it is believed that adequate use of oral tranquilizers, soporifics antipruritics (Temaril) and, when indicated, steroids should be made In addition, the indulgent, painstaking approach of the clinician resulting in good patient-doctor rapport is a cornerstone of successful management.

Lichen Simplex Chronicus. It is believed that this clinical entity characterized by cutaneous thickening, lichenification, and *persistently recurrent pruritus is deserving of special consideration* because of its frequency its manifestation in particular regions such as the anogenital areas (vulva, anus, and scrotum) nuchal area, and upon the extremities, and no matter where located, because of its extreme resistance to therapy

It is well to realize at the outset that such cutaneous expression is often a needed outlet for psychogenic disturbances and may represent a far less pathogenic threat to the individual than similarly induced intestinal ulceration, colitis, or nervous break down. There are many who argue, and perhaps rightfully so, that it is better to allow the individual this cutaneous psycho-

dynamic outlet than to remove it and precipitate a more disastrous consequence.

However there are a large proportion of patients exhibiting the clinical pattern of lichen simplex chronicus who benefit greatly by its removal, and in such instances every effort should be extended to obliterate the itch-scratch-lichenification sequence. If serious doubt exists as to the advisability of such cure the help of a psychiatrist in such determinations should be sought.

It has been amply demonstrated that the removal of scratch trauma will result in disappearance of the lesion of lichen simplex chronicus. However this cannot be obtained by the mere Do not scratch edict. Definitive substitution for scratching, accompanied by systemic therapy and conservative psychotherapy must be offered to the patient. To this end, topical anti pruritics ranging from lotions ointments, with or without steroids, as indicated by the presence or absence of significant inflammation, to topical freezing and x-ray therapy must be employed. The schooling of the patient in scratch substitution techniques is largely a matter of salesmanship Careful detailed explanation in the layman's terms of the itch-scratch-lichenification physiopathology accompanied by orientation and the prompt use of scratch substitutes such as cold compresses, application of lotions, creams, or ointments, at the proper time offer the patient a method and responsibility in effecting his own recovery

The adjunctive use of local freezing of lichenified areas offers much to the relief of localized pruritus. Ethyl chloride spray or Freon-114 as employed in dermabrasion for correction of facial scarring are effective tools for reducing lichenification rapidly The pruritic area is sprayed until a white frost is obtained and maintained for approximately 15 to 45 seconds, depending on the degree of lichenification A burning, stinging subjective response is induced, followed by a low grade inflammatory reaction. Superficial peeling usually follows and the process is repeated after all reaction has ceased, usually 3 to 5 days later and should be again repeated until lichenification is no longer present. Usually three such applications suffice to reduce the average area of lichenification to a thin, almost normal looking area of epiderm. Emollients

should not be applied during the inflammatory phase of reaction lest the peeling effect be reduced. Care must be taken to confine the freezing application to the lichenified skin and orifices, and mucocutaneous junction areas should be carefully screened to avoid unnecessary discomfort and injury. Another method of thinning the lichenified plaques and producing a local inflammatory response is the use of chemical peeling agents such as trichloracetic acid. The application of 20 to 30% trichloracetic acid by painting the plaque every 4 to 7 days results in a satisfactory peeling response. Care must be taken to confine the application to the lichenified area, and proper protection of the mucous membrane and orifices must be effected.

X-ray therapy is another modality in treating the lichenified pruritic plaque. Because of the chronicity and frequency of recurrence of lichen simplex chronicus roentgen therapy should be reserved for the specially trained therapist and should be employed in conjunction with various other modalities to ensure a lasting response. The repeated, indiscriminate use of x radiation may lead to serious degenerative sequelae.

Atopic Dermatitis. For the basic consideration of causation and management of this entity the reader is referred to other portions of this volume. However, inasmuch as pruritus is such a predominant and distressing symptom of atopic dermatitis, certain aspects are deserving of presentation and emphasis.

Perhaps here, more than in any other clinical aspect of pruritus, is treatment of the patient as a whole, rather than topical therapy to involved areas, a requisite of successful management. Time, sympathy, reassurance, and guidance are required in unlimited and at times unavailable amounts. Psychological factors are predominant and frequently not altered by even expert psychiatric attention.

The adequate use of systemic therapy such as tranquilizers, antihistaminics, sedatives, and careful steroid employment often change an antagonistic, resentful patient into a cooperative responsive individual. Symptomatic relief is a prime requisite, and to this end topical therapy as previously discussed may yield gratifying, although at times temporary, results. The use of

Temaril (2.5 mg three times a day with meals and 5 mg 1½ hours before bedtime) is often a valuable adjunct. This is particularly true in treating the adolescent and juvenile patient. For this purpose a liquid vehicle containing a dosage of 2.5 mg per teaspoonful is available. Dosage may be increased two- and threefold or even more when necessary to control itching, although the patient may be rendered a 24 hour sleeping subject by the use of higher dosages. During these periods of patient inactivity the repair processes may proceed without further damage of excoriation. Temaril has been found particularly useful in those frequent instances where oral steroid therapy must be employed to control acute, severe exacerbations of atopy By maintaining adequate levels of Temaril administration, steroid dosage may be reduced earlier and more rapidly without incurring "rebound" phenomena A similar observation has been made with the adequate use of tranquilizers for the same purpose, but our experience to date indicates that Temaril accomplishes this end even more regularly and satisfactorily

Topical therapy as applied to previously discussed acute, subacute, and chronic states of cutaneous reaction, apply equally in the management of the individual with atopic dermatitis. Similarly the principles of systemic therapy are also applicable in this instance, but it will be found that more frequent and discreet use of steroid therapy must be made to carry the patient over the more critical exacerbations. Barring definite contraindications to their use, steroids should be adequately used but always with watchful and constant supervision. The "hit and run" method appears preferable to prolonged high dosage relief gi ing regimens. Perhaps with the recent introduction of the newer steroid derivatives, longer periods of administration without undesirable sequelae may be available

SUMMARY

In summation it may be stated that the symptom of pruritus is often encountered, variously produced, difficult to manage, and at times resistant to all therapeutic measures. Immediate determination and removal of the cause while the most desirable and

effective measures, are unfortunately too infrequently obtainable Symptomatic relief with the use of external and internal agents then becomes the prime tool of the physician. To this end there are available for topical use baths, compresses lotions and liniments, paints, ointments and pastes, steroid-containing preparations, and the interdiction of known local sensitizing or primary irritants. Systemically sedatives, antihistaminics, tranquilizers, antipruritic agents, and oral and injectable steroids are available as adjunctives in therapy It appears that the judicious use of topical and systemic agents coupled with a high degree of patient doctor rapport offer the best prognosis for satisfactory relief while inciting factors are being determined and removed. Particular attention should be given to considerations discussed in those dermatoses inherently characterized by itching.

The following is a list of representative therapeutic agents which may prove of value in the treatment of a large percentage of pruritic patients.

APPENDIX Antipruritic Formulary

Topically In the acute wet stages primarily baths, compresses, lotions. In the subacute and chronic dry phases ointments, creams, paints and pastes.

Systemically As indicated sedatives tranquilizers, antipruritics, and steroids.

Topical

Baths
- Colloid
  - Linit starch (2 cups to ½ tub of tepid, 30–35 C water)
  - Oatmeal (2 cups boiled for 15 minutes, strained, added to ¼ tub of tepid, 30–35 C water)
  - Aveeno oatmeal (1 cup to tub of tepid water)
- Tars
  - Zetar emulsion (1–2 tablespoonfuls to tub)
  - Nu-Kol-Tar (2–4 oz to tub)
  - Ar Ex tar (2–4 tablespoonfuls to tub)
  - Juniper tar (2–4 tablespoonfuls to tub)

Compresses

Boric acid (tablespoonful per quart of tepid to cold temperature)

Burow's solution (1 16 dilution, tepid to cold)

Skimmed milk (tepid to cold, rinse off thoroughly)

Witch hazel (1:1 dilution, tepid)

Alibour's water (1 5 dilution, tepid to cold)

Silver nitrate (1% solution, tepid to cold)

Lotions, liniments, emulsions (to which may be added 1% phenol, ½% camphor ¼% menthol, 5–10% liquor carbonis detergens, or Nivea oil)

Calamine lotion

Mook's lotion

Pusey's Calamine liniment

Fluorohydrocortisone lotions (± Vioform)

Quotane lotion

Paints

Castellani's paint (Carbol-Fuchsin solution N.F) (half or full strength)

Silver nitrate (10% solution)

Ointments and creams (omit caine, antihistamine, and other potentially sensitizing substances)

Fluorinated hydrocortisone preparations (alone or in combination with antibacterial, antifungal agents)

Quotane

Tronothane hydrochloride

Dyclone

Eurax

Lassar's paste (for mechanical protection from irritating body excretions)

Systemic

Sedatives barbiturates, salicylates, bromides, chloral hydrate

Tranquilizers meprobamate e g Miltown, Equanil hydroxyzine e.g., Atarax, rauwolfia alkaloids, e.g., Serpasil, phenothiazines, e.g., chlorpromazine, Compazine.

Antipruritics Trimeprazine e.g., Temaril.

Steroids cortisone, hydrocortisone; prednisone, prednisolone; triamcinolone e g., Kenacort Aristocort.

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Paul LeVan

18

ACUTE AND CHRONIC URTICARIA

The majority of instances of urticarial reaction are acute, transient and relatively mild. They present little, if any therapeutic problem because of their innate self limitation. However acute severe urticaria accompanied by laryngeal edema and the more common chronic recurrent urticaria may present problems of the highest magnitude in their management. While considerable progress in symptomatic treatment has been made in recent years with the addition of effective antiwhealing agents and adjunctive medicaments, our understanding of the basic mechanism and the ability to determine specific causative factors leave much to be desired.

Statistical studies have placed the incidence of urticaria between 15 and 25% of the population [1] Because of the transient character of the majority of urticarial episodes, the actual incidence is not known. It is recognized, however that acute urticaria is particularly common in children and young adults, while the chronic type occurs more frequently in the middle-aged female With the advent of antibiotic agents, particularly penicillin, and the introduction of new groups of chemical therapeutic substances, it appears from voluminous literature that the

incidence of urticarial response to medication has increased in the past decade [2] With continued use of the more recently introduced drugs, this trend may be expected to continue as time for the development of sensitization elapses. Similarly angioneurotic edema, which is regarded as a tissue reaction akin to that of urticaria, appears to follow the same general trend. The site of shock tissue in angioneurotic edema is primarily in the subcutaneous vessels as contrasted to the involvement of the vasculature of the upper corium occurring in urticaria. The difference in site of vascular reaction is offered as the explanation for the difference in clinical appearance and degree of pruritis in the two similar reactions. As might be expected, deeper vessel involvement with a subsequent edematous reaction occurring in angioneurotic edema results in a diffuse process often manifested by asymmetrical swelling of the lip or eyelids. In contrast, urticaria, per se, usually presents circumscribed edematous pruritic lesions. Coalescence of these primary elements may eventuate in large plaques constituting giant hives.

MECHANISMS

The exact mechanisms of urticarial wheal production remain incompletely understood. A review of current literature presents theories based on suggestive, but not necessarily conclusive, evidence. As set forth many years ago the triple response of Lewis [3] which propounds that release of H substance with subsequent increased vascular permeability results in the production of whealing, remains the most widely accepted theory Lewis H substance as originally suggested is now generally recognized as being histamine itself Several investigators have shown that this substance arises from the tissue mast cell granules and its release may be brought about by numerous substances and factors. Further support of the histamine theory is derived from investigations of the nettle plant (*Urtica urens*) [5] whence the disease takes its name. This plant contains significant amounts of histamine and acetylcholine. Introduction of these chemical substances directly into the skin produces a reaction identical to that of nettle rash. Perfusion of the skin with histamine also demon-

strates an alteration of capillary permeability resulting in edema of the tissues [1] The experimentally and clinically proved ability of antihistaminics to prevent wheal formation following injection or electrophoretic introduction of histamine [6 7 8] likewise supports the theory of the role of histamine in the production of urticaria. While this evidence may not be wholly conclusive and the observed response to antihistaminic drugs may be due to pharmacodynamics other than direct antihistaminic action, the preponderance of evidence to date points toward this suggested mechanism.

Accepting the release of histamine as a major pathogenetic factor in the majority of instances of urticaria production, attention is directed toward the possible trigger mechanisms which are believed to affect histamine release. Allergists and immunologists have long regarded antigen-antibody reaction as one of the prime producers of histamine release. Further recent attention has been focused on a large group of substances found capable of acting as histamine liberators [1] Most of the studies have employed Tween (sorbitol monolaurate) dextran, morphine, and curare as liberators, but this effect has also been evidenced by the following variety of substances

- Peptone
- Trypsin
- Lysolecithin
- Animal venoms
- Bacterial toxins
- Strychnine
- Lichenisormin
- Diamines
- Diamidines
- Diguanidines
- Diisothioureas
- Diquaternaries
- Propamidine
- Papaverine
- Codeine
- Thebaine
- Apomorphine
- Horse serum
- Egg white antigens
- Pethidine
- Polymyxin
- Polyvinylpyrrolidone

In addition to the above there are other stimuli such as heat, exercise, and psychogenic factors, all unassociated with immunologic response or direct histamine liberation, which can produce urticaria [9] Investigation has shown that the release of acetyl choline is the trigger mechanism in the development of wheals from heat and exercise. Experimentation has also demonstrated that central stimulation of the nervous system eventuates in the

sending out of impulses via the cholinergic fibers of the autonomic nervous system resulting in the release of acetylcholine. The term *cholinergic* urticaria has been applied to this segment of whealing reactions Most observers believe that cholinergic urticaria is triggered by acetylcholine which in turn causes release of histamine. This is borne out by the failure of acetylcholine to produce urticaria in histamine-exhausted tissue. However this point still remains open to argumentation, and further investigation of this mechanism is desirable.

CLINICAL DIAGNOSIS

The clinical diagnosis of urticaria seldom presents a problem. The physical characteristics particularly the evanescent nature of the lesions and the accompanying pruritis, usually enables even the layman to make the diagnosis. In the more chronic form, the cyclic reappearance of the lesion and the not infrequent association of psychogenic stimuli with resultant crops of wheals are characteristically peculiar to this type of urticaria. Special forms of urticaria such as dermographism, erythema multiforme, papular urticaria of childhood, angioneurotic edema, and urticaria pigmentosa should be recognized by their individual characteristics, so that fruitless investigation in the improper direction may be avoided. A diagnosis of dermographism is suggested by the appearance of wheals at sites of friction or trauma and the ready production of urticaria by stroking the skin. Several observers have commented about the apparent frequency of dermographism in patients who have previously experienced a penicillin urticarial reaction [10] Erythema multiforme in which wheals predominate will also usually present other types of lesions, a distribution pattern, and a history suggestive of this diagnosis. Papular urticaria in childhood is now generally recognized as a reaction pattern to flea or insect bites in most instances. The papular character of the lesions, their intense pruritis, and relative persistence are aids in diagnosis. Angioneurotic edema usually occurs about the face or upper parts of the body rather than in the dependent portions. It is asymmetrical, is tran

sient as compared with the edema due to lymphatic obstruction (elephantiasis nostras, lymphedema) and is not infrequently accompanied by urticarial wheals on other parts of the body

CAUSAL DIAGNOSIS

As noted above, clinical diagnosis rarely presents difficulty but the opposite is true of the establishment of a causal diagnosis. Inasmuch as the satisfactory management of the patient with urticaria depends primarily upon the removal of the cause maximum endeavor should be extended in this direction In acute urticaria the offending agent is often obvious and not infrequently suggested by the patient. However in the chronic recurrent type the establishment of a causal diagnosis may call for the utmost effort on the part of both physician and patient. All too often, despite exhaustive search no offending agent can be detected, and these patients are labeled as having a psychogenic urticaria, although this conclusion may be quite erroneous.

As a practical approach to the problem initial history taking may be directed toward the four main causative categories which account for the largest incidence of urticaria. These are drug allergy food allergy infection, and psychic factors. Should the history carefully taken in reference to these four causative categories, fail to reveal a causative factor then a more broad approach must be utilized based upon a thorough study of the numerous substances known to produce urticaria As an aid in such an approach the following causative classifications of urticaria may be of some assistance

Nonallergic Urticarias

The nonallergic urticarias are those whealing reactions resulting from a substance in the blood stream acting directly on vessels or through the release of histamine from mast cells, but presumably not because of an antigen-antibody interaction. Five groups of factors have been placed in this category drugs parasites, physical agents, other diseases and neurogenic and psychogenic factors.

Drugs. These substances may produce a nonallergic response when introduced into the skin or blood stream by causing the release of histamine from the mast cells. An extensive list of substances acting in this manner has been presented earlier in this chapter. Among the more common drugs are morphine, opium, alkaloids, atropine, quinine, thiamine, and pilocarpine. These do not act as allergens but when present in sufficient concentration will effect the release of histamine. This substance itself introduced into the circulatory system or skin will cause urtication by direct action on the blood vessel wall, and the reaction may be sustained because the presence of histamine may cause the release of additional amounts of this substance from the mast cells.

Parasites. Parasitic infestation may act on man through a nonallergic mechanism and produce urticaria. Bee stings and insect bites may also cause this reaction in the same manner. Hairs of the brown-tail moth, leeches, and jelly fish may produce urticaria by contact. This mechanism is distinct from frequently seen allergic response to flea bites, mosquitoes, and plants.

Physical Agents. Such factors as cold, heat, trauma, and radiant energy may produce nonallergic urticaria. Dermographism is a long recognized type of skin response to local trauma and is attributed to local release of histamine.

Other Diseases. Skin and systemic diseases may manifest themselves in urticarial fashion. Lymphomas, urticaria pigmentosa, liver disease, carcinomatosis, intestinal parasites, lupus erythematosus, malaria, rheumatic fever and kidney involvement may all express themselves cutaneously in an urticarial response of a nonallergic nature.

Neurogenic, Psychogenic Factors. Neurogenic urticaria comprises a large and not too well understood segment of the urticarial reaction group. Tension states, excitement, anxiety, emotional stress, and particularly resentment all appear capable of producing urticaria in certain individuals. It is apparent that a variable threshold exists in humans, for no amount of the above stimuli will produce urticaria in some individuals, while in others a minute degree of psychic stimulation will result in a severe

response Cholinergic urticaria, which is presumed to be elicited by the release of acetylcholine at nerve endings, may be the *modus operandi* in the neurogenic group. However clear-cut evidence of the pathogenesis of this type of urticaria is still lacking, and further investigation along this line is desirable

Allergic Urticarias

Histamine release as the result of antigen-antibody reaction appears to be the most probable mechanism of production of allergic urticaria. This may be brought about by hypersensitivity to inhalants, ingestants, injectants, external contactants, and focal infections.

Inhalants. Feathers down, horse hair and various fillings of pillows and mattresses, pollens, animal dander clothing dust (silk) tobacco smoke cosmetics such as perfumes and powders, medicinal sprays, insecticides, volatile compounds, and fungi may all enter the body through the respiratory tract and give rise to allergic response.

Ingestants. Foods are a very common causative factor in acute urticaria but not as frequent in causing chronic whealing. The most common offending foods encountered are strawberries, shell fish, fish, cheese, nuts, chocolate, wheat, eggs milk, and pork. Less common offenders may be found in almost any food product.

DRUGS. The slogan Any drug by any route at any time may produce urticaria is a good tenet to follow Special reference to drugs will be discussed under Management.

Injectants. Vaccines, serums, allergens for diagnosis or treatment, insulin, epinephrine and a host of other substances have been indicted as causative agents of urticaria. Frequently protein contaminants are responsible for the reactions encountered rather than the active therapeutic factors. Blood transfusions and insect and bee injections may also produce severe allergic response.

External Contactants. These substances are infrequently responsible for urticarial reaction. While it is more common to observe a contact type of eczematous dermatitis because of these factors, the production of whealing has been observed following exposure to cosmetics, clothing, particularly nylon, plants, chem-

icals, foods, and hair Such allergic whealing responses seem to occur more frequently in individuals with atopic hypersensitivity

Infections. The nonallergic type of response may often be elicited by this factor as previously noted Focal bacterial infections, trichophyton infections with id" reaction, and parasitic infestation have all been indicted in producing allergic urticaria.

MANAGEMENT

Since the most effective treatment measure in the management of urticaria is removal of the causative agent or agents, unlimited effort and zeal should be expended to this end. The basic step in approaching the problem is the procurement of a detailed history aimed at elucidating the type of urticaria and the probable or possible causative factors concerned.

Drug histories must be given special attention and questions presented in a variety of ways utilizing the most basic and simple lay terms. A useful approach is to question along the lines of a systemic review Not infrequently medications taken for long periods in habit fashion will be brought to light. Products such as vitamins, nutrient supplements, bowel regulators, appetite reducers and the like are not regarded by the patient as medication. It must be borne in mind that milk, as well as chicken, may contain sizable amounts of penicillin because of the feeding of penicillin to cattle or fowl for the prevention or treatment of infection. Similarly cognizance should be taken of the presence of penicillin in polio and other vaccines.

History taking regarding foods does not present as great a problem as encountered with the search for offending drugs. Suggestions regarding evaluation of causative foods and the use of a diet are discussed later in this section Continued history taking should include a search for clues regarding internal or external parasitic infections, the effect of physical agents (such as sun, heat, cold) exertion systemic diseases, psychic disturbances, inhalants, ingestants other than food and drugs previously discussed, injectants, contactants, and infections.

As an aid to history taking a detailed daily diary may prove valuable in establishing a causative agent. This should not be

restricted to a dietary and drug record alone but should include information regarding all the aforementioned possible factors.

Generally speaking, scratch and intradermal testing rarely offer aid in determining causative agents in chronic urticaria. Occasionally a patient with marked hypersensitivity may successfully be tested with selected materials such as animal hair or dander. The patch test may be utilized with some success where external contacts are suspected and probable substances are applied to the skin. Adhesive tape and dyes may elicit urticarial response when so tested.

In those numerous instances where history and testing fail to indicate the offending substance, attention must be directed to the empirical elimination of the two types of most frequently encountered offending agents—drugs and food.

While basic foods and their newer products have remained essentially the same for many years, the opposite is true of drugs. Many new types of drugs have been introduced in recent times, and even those affording us limited experience have already indicated their urticariogenic capacity. The antibiotics, particularly penicillin but extending almost throughout the fungous product realm, have demonstrated this capacity to a great extent [11, 12]. Insulin [13, 14], liver [15] preparations, antimalarials, heparin [16] and a host of other recent preparations have likewise been implicated as causative agents of urticaria. By way of paradox, even antihistaminics such as pyribenzamine [17] and Chlor-trimeton along with others and the steroids, ACTH and cortisone, have been reported as capable of producing urticaria due either to species or organ specificity [18, 19]. This property of the usually antiwhealing agents must be kept in mind in history taking and evaluating failure of response to therapy in the patient with chronic urticaria.

Since skin testing for drug sensitivity has proven unsatisfactory and at times misleading, in the majority of instances clinical observation of response following removal or introduction of the drug in question remains the more reliable approach to the problem. The patient should be instructed to eliminate all nonvital preparations previously used. This refers not only to ingested

drugs but those administered by any other possible route. Vaginal, rectal, nasobronchial, and urethral avenues must be included, for occasionally a contraceptive cream, a douche, a suppository a spray or bladder instillation may give rise to recurrent urtication. In pursuance of the elimination of possible causative agents, such preparations as dental creams, particularly with new antidecay elements added, medicated chewing gums, oral washes, gargles, topical preparations, vaccines, toxoids and toxins, pollen testing substances, and many others should all be interdicted during the observation period.

In contrast to the task of total avoidance of drugs the elimination of potential causative foods is more readily accomplished. Initially the patient should be questioned as to his own suspicions based on cause and effect observations. Gastrointestinal intolerance, inexplicable food dislikes, and new food products he has ingested should all be brought forth in the history Not infrequently information so obtained will terminate further search. In acute urticarias sea foods, nuts or nut products, and a variety of berries will be found responsible for the onset of whealing shortly after their ingestion. In chronic urticaria the causal picture may not be so clear inasmuch as allergens, e.g milk and its products, beef certain vegetables may not produce hives for several or even 24 hours after their ingestion, thereby clouding the cause and effect relationship [20] A carefully detailed diary kept by the patient may be of great diagnostic assistance in crystallizing causal conclusions. An additional complicating factor is introduced by the ability of combinations of foods rather than a food alone to produce allergic response. As in the evaluation of the causative role of drugs, the history of many years of ingestion of certain foods should not be accepted as negative evidence Again, the basic premise that anyone may become sensitized to any substance of any kind still remains a cornerstone of diagnostic evaluation

Except for the informative results often obtained by skin testing to nuts and sea foods in acute urticaria (when such testing is not often necessary in determining the offending agent) skin tests of foods have not been overly helpful in causal diagnosis.

While they may be used adjunctively for investigative guidance the elimination of suspected foods and subsequent clinical response remains the more reliable and rewarding approach to the problem.

To accomplish such evaluation of food factors, a printed basic diet is given to the patient and the importance of meticulous execution is stressed. A sample diet such as one containing any beef rice in any form, and canned pears or apples will provide a good base line upon which to proceed. Single foods are added at 48- or 72 hour intervals and the urticarial pattern observed and recorded. The reader is referred to standard dietary references for further guidance.

During the above drug and dietary restriction, other factors such as psychic influences, particularly emotional disturbances, should be constantly watched for and evaluated. Such psychogenic evaluation is often difficult and apt to be misleading, so that expert consultation may be required. The not infrequent observation of psychogenic factors present in urticarial patients has all too frequently led to an erroneous diagnosis of neurogenic urticaria long before a systematic search has been accomplished. It must be recognized that many patients with chronic urticaria exhibit emotional disturbances as a result of their affliction rather than as the cause of it. Similarly the very drug or faddist food they may ingest to control their symptoms may in fact be causing them to persist. Further nervous tension is believed to render an individual more susceptible to urticarial response by altering his threshold of reaction This is attested to by the not infrequent history of disturbances of the psyche just prior to the onset of urticaria, the causative agent of which is later identified as nonpsychogenic. Likewise the apparent effect of sedatives and ataractic drugs in raising but not abolishing the threshold of urticarial reaction suggests that neural tensions are a contributing factor Further study of this phase of pathogenesis is desirable.

The production of urticarial response by psychic stimulation has been both clinically and experimentally observed [21, 22] by several clinicians and investigators. Graham and Wolf [23] have demonstrated the effect of psychic stress, particularly resentment,

in increasing skin reactivity However Sulzberger and Baer [24] raise several pertinent questions as to the actual production of urticaria per se Kepecs, Robin, and Brunner [25] observed increased exudation of fluid in subjects placed under emotional stress. Although the exact mechanisms involved are still a matter of debate [26] the existence of cholinergic urticaria appears to be widely accepted at this time. It is supposed that psychic stimuli traveling along the autonomic nervous system effect the release of acetylcholine of nerve endings. This substance in turn causes the release of histamine from the mast cells.

Continuing the search for causal factors, a careful physical examination should be accomplished. Evidence of such systemic diseases as previously set forth may be uncovered so that appropriate laboratory studies and indicated consultation may be procured. Investigation of physical evidence indicating infection should be directed particularly to common sites such as teeth, tonsils, sinuses, prostate and urinary tract, pelvis, and gallbladder Urticarial response to such infection may be a result of either the affected tissue reaction product or the bacteria and their metabolites. A high eosinophilic count in the peripheral blood of patients with chronic urticaria should direct attention to a thorough search for intestinal parasites.

In the course of the physical examination some causal clue may be obtained from the clinical appearance of the skin lesion. For example, drug sensitivity will frequently produce wheals with a violaceous hue and serpiginous borders occurring on the trunk. Large urticarial lesions showing progressive central clearing and an advancing peripheral border are often associated with penicillin sensitivity Deep-seated, persistent, burning or stinging hives are said to be produced more often by a response to infection, while grouped, small, pruritic wheals with an erythematous halo are frequently of cholinergic origin. The cyclic occurrence of lesions after 5 P.M. daily with disappearance in the morning is often evidence of their neurogenic nature. Linear configuration on exposed surfaces is more often associated with a contactant. Physical exertion tends to produce whealing more prominently over the back, chest, and neck. The foregoing physical charac-

teristics are merely suggestive and are not considered causatively pathognomonic.

The institution of symptomatic treatment may be indicated at variable times in the management of the urticarial patient. Recent onset of symptoms, their severity and the patient's physical or psychological reaction to his disease may demand immediate or early suppressive therapy In acute urticaria such treatment when carried out as suggested below will usually suffice to terminate the attack, and a cursory history will often reveal the offending agent However in chronic recurrent urticaria symptomatic treatment may be advisable initially for a short period of time while history taking and basic observations are being accomplished. As the investigation proceeds, it may be necessary to terminate active therapy or substitute placebo medication, so that pertinent observations may be made of the effect of diet, drugs, and other causative possibilities. The management of the patient must be individualized to the type of person, his previous medical experience with his disease and the severity of the symptoms. Every effort to establish and maintain good rapport must be made for it is essential to successful management of the patient with chronic urticaria.

Once the urticarial syndrome has been terminated, either spontaneously or as the result of investigation and therapy attention should be given to the prevention of recurrence This is an important objective inasmuch as the patient who experiences a repetition of his urticarial reactions on numerous occasions not only will become agitated and difficult to manage, but his reactions may be elicited at a lower threshold of excitation and may become more severe. In addition he may become refractory to certain drugs and dosages previously found therapeutically effective.

Prophylaxis is often aided by education of the patient to careful avoidance of suspected or proved causal agents and related substances. Intermittent use of some of the adjunctive measures noted below particularly those directed toward lessening nervous tension and emotional stress may prove of value in aborting an impending recurrence.

In selected instances desensitization to implicated causative agents may be accomplished by the administration of subclinical amounts of the substances, gradually increasing dosage over a period of time. However this is often a tedious and difficult task for both patient and physician. This technique perhaps is of most value in the relatively infrequent inhalant produced urticarial patient, and in those violently reactive to insect bites such as the bee sting.

TREATMENT

The necessity and importance of causal diagnosis and subsequent elimination have been previously emphasized. Regardless of the physician's success or failure in accomplishing this phase of management, symptomatic relief must be given the patient. To this end there are fortunately available several therapeutic agents of different chemical nature which show in common their ability to counteract the urticarial response or to alter the reaction threshold. Their judicious use individually or in varying combinations will afford symptomatic relief in a large portion of instances. This is particularly true in acute urticaria where the offending substance has been eliminated from the body and not reintroduced. In chronic recurrent urticaria, however they may eventually prove less effective, and doses may have to be altered as tolerance is built up and/or undesirable side reactions appear It must be borne in mind that symptomatic treatment does not alter the basic pathogenesis of urticaria and upon cessation of therapy recurrence is possible if not probable.

The therapeutic agents may be divided into specific anti-whealing drugs which either prevent, ameliorate, or speed resolution of urticarial wheals, and the adjunctive medicaments which alter threshold response or afford symptomatic relief.

Specific Drugs

Adrenergics. Until recent years epinephrine has been the most widely used histamine antagonist. With the advent of other therapeutically effective agents, its use has become less popular It still remains one of the best pharmacological antagonists of

histamine and despite unpleasant side reactions it is probably the most effective single drug controlling acute, severe urticaria. The major drawback of epinephrine is its rapid oxidation in the body so that repeated administration is necessary thus rendering it undesirable in chronic recurrent urticaria. A hypodermic injection of 5 to 10 mm of 1:1,000 solution will usually bring response. However this dosage may have to be repeated at intervals as short as 1 to 2 hours in severe cases, especially if other antihistaminic substances are not available. A longer period of effectiveness may be obtained by using a solution of epinephrine in oil, in propylene glycol alginate or in glycerin and sodium thioglycolate. A dosage of 10 to 15 mm of epinephrin in oil will frequently last 4 to 8 hours. Unfortunately because of pressor effects, it is contraindicated in hypertension and cardiac disease Epinephrine is of more use in acute urticaria, particularly that accompanied by laryngeal edema than in the treatment of chronic urticaria. In addition to its direct effect upon blood vessel walls and their permeability White suggests that epinephrine may also cause an increase of ACTH release [27] Ephedrine salts alone or in combination with other drugs have also been utilized in the past as antiurticarial agents Their use has been all but discarded with the availability of more effective drugs.

Antihistaminics. Since the advent of the antihistaminic drugs the treatment of urticaria has been considerably enhanced While these substances are not as effective as epinephrine in resolving urticarial wheals, they do prevent or ameliorate the formation of new wheals most effectively This is presumably accomplished by blocking the action of histamine Because they possess no pressor effect, they may be used in hypertensive and cardiovascular disease patients. Further their sedative and soporific side effects are often desirable in the management of the urticarial patient

The selection of which of the numerous antihistaminic drugs to use is largely a matter of personal experience and preference Two factors should be considered in the use of any of these agents first, the presence of undesirable or desirable side effects of the drugs *in the particular patient being treated and, second*, the use of adequate dosage to afford maximum antiwhealing ac-

tivity As previously noted, such accompanying effects as drowsiness and sedation are often of great value in the management of the patient. On the other hand, these same effects in the ambulatory car-driving individual may be dangerous and contraindicated. Dosage often must be doubled over the usual amounts employed to obtain satisfactory response in severe cases, and when refractoriness is evident, a change of drug is indicated. Following remission, it is often advisable to maintain the patient on an antihistamine regimen for several weeks, thereby diminishing the possibility of recurrence. Fortunately experience to date has indicated that the antihistamines are well tolerated and may be administered over extended periods of time. In addition to oral use, these drugs may be given by subcutaneous, intramuscular or intravenous routes. The latter may be desirable in acute severe urticaria, since the onset of antiwhealing action has been shown to be more prompt by the intravenous route [28] Parenteral Chlor Trimeton (0.2 ml of the 100 mg per milliliter solution) or Benadryl (2 ml of the 10 mg per milliliter solution) repeated at 3- to 4-hour intervals may be useful, particularly if gastrointestinal upset interferes with oral administration.

Steroids. For severe acute cases not responding to antihistaminics and where epinephrine is either contraindicated or produces unpleasant side effects, ACTH and cortisone will be found to be of great benefit in tiding the patient over the peak of his allergic response. ACTH gel, 60 I U intramuscularly daily or oral prednisolone, 20 to 40 mg per day decreasing as rapidly as response will allow is often of great symptomatic benefit in stubborn or severe urticaria. As with antihistaminics, adequate dosage should be employed to effect relief but unlike these drugs, prolonged administration is inadvisable because of the well-known adverse effect of prolonged steroid medication. However intermittent usage for short periods, the so-called "hit and run method, in the treatment of severe exacerbations of acute or chronic urticaria is a useful and effective procedure. In the acute severe case initial intra enous use of ACTH followed by a gel preparation or oral cortisone has been recommended by some authors. This practice should be limited to extreme in-

stances, for the intravenous use of ACTH is not without danger [29] Steroid therapy in patients with urticaria of unknown cause should be reserved for urgent situations, inasmuch as underlying disease processes responsible for the urticaria may be adversely affected by the use of steroids. Topical application of steroid containing ointments are of little value if any in controlling urticarial symptoms.

Enzyme "Neutralizers. Zimmerman [30] Becker [31] Chen [32] and Minno [33] have found the enzyme penicillinase, first identified by Abraham and Chain in 1940 [34] a highly effective means of eliminating the antigenicity of penicillin. They found its use to be superior to suppressive therapy of penicillin reactions. Basically penicillinase hydrolyzes penicillin into penicilloic acid, a presumably nonantigenic compound. Clinical application, according to these authors, supports this contention, as shown by the results obtained with penicillinase in patients experiencing penicillin reaction. Twenty four to forty-eight hours is usually required for clinical response, and in the presence of depot penicillin injections the penicillinase may have to be administered at 4 to 5-day intervals. An approximate ratio of 1 unit of penicillinase for every 20 or 25 I U of penicillin administered is required to obtain satisfactory response in most instances. In acute emergencies such as anaphylactoid shock, sufficient time may not be available to neutralize the antigenic agent. However where the patient can be temporarily sustained by the use of pressor substances, the enzyme may prove valuable in subsequent management of the reaction. Hence, a substance may be available for therapeutic or prophylactic use when penicillin-containing vaccines are used or if penicillin is the only available antibiotic for a known penicillin-sensitized individual. This enzyme preparation also may be used for differential causal diagnosis because of its specificity according to Zimmerman [30] However further clinical study is desirable to establish the true role of penicillinase in the treatment of penicillin-induced urticaria.

Adjunctive Medication. SEDATIVES. The time-honored drugs used for sedation have consisted primarily of barbiturates, bromides, and chloral hydrate These substances are frequently

found to be unsatisfactory because of habit formation, development of tolerance, unpleasant side reactions such as "hang-over" pruritis and skin eruptions, and occasional excitation of the patient rather than a sedation effect. Although new sedative agents have been developed which do not possess the aforementioned undesirable properties, their general and popular use has been somewhat delayed because of the sedative effects observed with the use of the antihistaminics and the tranquilizers. The use of these two agents in the management of urticaria usually provides adequate sedation as a side reaction.

TRANQUILIZERS. The use of this group of newer adjunctive agents has improved to some degree the management of the urticarial patient. Inasmuch as many bouts of urticaria are accompanied by psychogenic disturbances either as a cause or an effect, any agent which tends to minimize these factors is a desirable therapeutic adjunct. Clinical studies [35] have demonstrated a lessening of neural tension, emotional instability, and have rendered the patient more easy to manage. While these ataractic drugs are not without undesirable side effects, particularly depression and excessive drowsiness in certain patients, a widening choice of tranquilizing agents is appearing. At the time of this writing, four major groups of tranquilizing drugs are available. They may be classified as follows:

1. Rauwolfia alkaloids (reserpine—e.g., Serpasil, 0.25 mg four times a day)
2. Phenothiazines (chlorpromazine—e.g., Thorazine, 25 mg four times a day)
3. Propanediol dicarbamate (meprobamate—e.g., Equanil, 200 to 400 mg four times a day)
4. Diphenylmethanes (hydroxyzine—e.g., Atarax, 10 to 25 mg four times a day)

As with the antihistaminic drugs, dosage of the above medications must be individualized, and the quantitative suggestions stated above may have to be considerably altered in certain instances. When symptoms of intolerance, undesirable side effects, or the building up of tolerance appear, a change to a tranquilizer of another chemical group is indicated and may be readily ac-

complished without marked loss of tranquilization. In recent clinicodermatologic studies of four chemically different tranquilizers, the authors findings based upon consistency of response, average degree of tranquilization, and frequency and severity of side reactions indicated that meprobamate (Equanil or Miltown) and hydroxyzine (Atarax) preparations were preferable to the rauwolfia (reserpine) and chlorpromazine (Thorazine) drugs

In several instances where tranquilization was sought, we found it advantageous to give one and one-half times to twice the usual daytime dosage per each meal and before bedtime. Even larger bedtime doses may be used if necessary for the soporific side effect presents no problem as encountered in administering larger doses during the day As with the use of all drugs, untoward reactions, particularly in the allergic patient, must be carefully watched for and if present may be dealt with by changing to a tranquilizer of a different pharmacologic group.

A newer phenothiazine derivative, Temaril (2.5 mg four times a day) is at present undergoing clinical investigation. This drug is said to exert unusual antipruritic properties [36] particularly in pruritis involving a strong neurogenic factor The authors limited experience to date using Temaril seems to demonstrate greater antipruritic activity in a variety of dermatoses than that obtained with the above listed tranquilizers or antihistaminics. In addition, an antihistaminic and tranquilizing effect has been evident in those patients afforded relief from pruritis by the administration of Temaril. Further investigation of this drug is proceeding and will be reported at a later date.

MISCELLANEOUS ADJUNCTIVE THERAPY Intravenous procaine has provided temporary relief in some instances of urticaria, but its use is not without danger Five hundred cubic centimeters of a 0.1% solution are administered slowly by the intravenous route. In view of more recent and effective drugs its use is not recommended Calcium intravenously although used for many years, has rarely proved to have any beneficial effect except, perhaps, a psychological one. Nicotinic acid recommended by several authors has likewise failed to stand the test of time. Vitamin K,

vitamin C, vitamin B, and vitamin D have all been recommended for use in urticaria, but no sustained beneficial results have been obtained by most investigators. Autohemotherapy cobra snake venom, intravenous histamines, Piromen injections, heparin, and many other recommended adjuncts have largely fallen by the wayside. Intravenous aminophylline still has its supporters but, with the use of newer therapeutic modalities, appears destined to be relegated to the past. Topical therapy such as antipruritic lotions and colloid baths, although frequently used, do not alter the clinical course. However they may afford some degree of symptomatic relief and are worth trying.

SUMMARY

In summary it may be stated that the satisfactory management of urticaria depends primarily on establishment of a causal diag nosis. Unfortunately this proves impossible in about 50 per cent of the instances of chronic urticaria. The administration of drugs for symptomatic relief then becomes the prime tool of the physician. To this end he fortunately has available the adrenergic drugs, antihistamines, steroids, sedatives, and tranquillizers, and, possibly the enzyme penicillinase for penicillin-induced urticaria. Following termination of a bout of urticaria, prevention of recur rence must be attempted, based upon the information and ex perience gained in the management of the patient at hand.

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Harold Price

19

PEMPHIGUS

In the past the label of *pemphigus* applied to a cutaneous eruption carried with it a most serious prognosis, for the majority of individuals afflicted sooner or later succumbed. The therapeutic measures employed were, for the most part, ineffective—the results extremely discouraging. Here and there an occasional patient might manifest a remission, or perhaps a cure, either spontaneously or seemingly in response to some particular therapeutic attack. This unusual turn of events would invariably bring up the question as to whether pemphigus was, in fact, the correct diagnosis.

DIFFERENTIATION FROM OTHER BULLOUS DISEASES

The *differentiation* of pemphigus from other similar-appearing bullous eruptions was not clear-cut, for the diagnosis depended largely on the clinical features and course of the disease. That the microscopic features could not be relied upon for diagnosis is indicated by the following statement by Becker and Obermayer [1] "In none of the forms of pemphigus are the histologic changes sufficiently characteristic to allow a diagnosis per se Similarly in his first edition of "Histopathology of the Skin [2]

Lever stated "The various forms of pemphigus with the exception of pemphigus vegetans show no diagnostic histologic picture. The vesicles and bullae (pemphigus vulgaris) are found usually in subepidermal, but occasionally in intraepidermal, location.

Clarification of this somewhat confusing situation was sorely needed. A beginning in this direction was provided in 1943, when Civatte [3] described a microscopic lesion which he considered specific for pemphigus. Confirmation of this observation by many others gradually followed, and it is now generally accepted that the early microscopic lesion of true pemphigus is a nontension, acantholytic, intraepidermal bulla. Acantholysis refers to the loss of coherence between epidermal cells due to degeneration of the intercellular bridges, leading to the formation of clefts and bullae within the epidermis. Individual loosened and altered epidermal cells (acantholytic cells) as well as some in groups, are found floating in the intraepidermal cavity Other bullous eruptions which might be confused with pemphigus, such as erythema multiforme, dermatitis herpetiformis, and bullous drug eruptions, are characterized by subepidermal pressure bullae without acantholysis. Thus, on the basis of characteristic microscopic features, the diagnosis of pemphigus would appear now to rest on fairly secure ground.

However there still occur bullous eruptions to baffle the physician, eruptions which clinically resemble pemphigus vulgaris quite closely but which present microscopically a subepidermal bulla. These have recently been classified as bullous pemphigoid by Lever [4] and pemphigoid by Rook and Waddington [5] and are considered as relatively benign diseases, separate from true pemphigus. The problem that arises here is that some of the patients follow a downhill course like that of pemphigus. Twelve of thirty-eight patients diagnosed as pemphigoid in Rook and Waddington's group died after an average duration of 14.5 months. It is only fair to state, however inasmuch as many patients with pemphigoid are either very old or already in poor health, that the cutaneous disease may well be only contributory to death and not the essential cause.

Histopathology Can pemphigus vulgaris be differentiated from pemphigoid on the basis of histopathology? To answer this question Fisher [6] reviewed the cases of 56 patients diagnosed as pemphigus vulgaris. Acantholytic intraepidermal bullae were demonstrated in some patients, in others, only subepidermal bullae were found, even after repeated biopsies. He arrived at the following conclusions

1 While the finding of an acantholytic intraepidermal bulla is diagnostic of pemphigus vulgaris, its absence does not rule out the disease.

2. There appeared to be no direct correlation between the clinical features, course of the disease and the histologic findings.

From this it would appear that some patients with subepider mal bullae exhibit the clinical features and course of true pemphigus. Other reports [7 8] have also indicated that difficulty is sometimes encountered in differentiating pemphigus from pemphigoid. In this regard, it should be pointed out that repeated biopsies may be required before the acantholytic, intraepidermal bulla of pemphigus can be demonstrated. The likelihood of finding this lesion is greatly enhanced by selection of early and small vesicles for biopsy

While significant advances have been made in the differentiation of bullous disorders, causation for the most part continues to be elusive and many puzzling elements remain to be solved. The following present-day classification of the pemphigus group of diseases may afford some clarification

CLASSIFICATION OF THE PEMPHIGUS GROUP OF DISEASES

I. Pemphigus
   A. Characterized by intraepidermal acantholytic bullae.
   B Several variants exist and transition from one form to another occurs.
      1 Pemphigus vulgaris.
      2. Pemphigus vegetans.
      3. Pemphigus foliaceous.
      4. Pemphigus erythematosus (Senear Usher)
II. Pemphigoid
   A. Characterized by nonspecific subepidermal bulla
   Not true pemphigus.

B Two variants.
1. Bullous pemphigoid—pemphigoid—benign pemphigus.
   a. May follow same course of pemphigus vulgaris.
   b Atypical forms of erythema multiforme, dermatitis her petiformis, and bullous drug eruptions should be considered.
2. Benign mucous membrane pemphigoid—ocular pemphigus—pemphigus conjunctivae.
   a. May have associated cutaneous lesions with mucous membrane involvement.

III. Familial benign chronic pemphigus (Hailey Hailey)
A. Microscopic lesion may resemble that of pemphigus.

Pemphigus acutus (acute febrile grave pemphigus) and Butcher s pemphigus, formerly considered as variants of pemphi gus, are now considered to be instances of fulminating pyoderma, toxic eruption, or severe erythema multiforme. The term *pem phigus neonatorum* is no longer valid, as it is now recognized as a severe form of bullous impetigo

TREATMENT

Steroids. Prior to the advent of steroid therapy the management of the patient with pemphigus was a most unhappy and depressing problem, as no form of therapy offered any consistent or significant measure of aid. In sharp contrast, the gratifying and often dramatic response to present-day treatment is a most satisfying experience, for in the vast majority of patients, satis factory control of the disease can be accomplished readily and quickly by adequate treatment with corticotropin and corticosteroids. Although it has been reported that a small percentage of patients have had remissions for a number of years after therapy was discontinued, it is by no means suggested that this therapy is curative. As a rule maintenance doses of steroids must be continued indefinitely to prevent recurrence.

The first objective of therapy is to suppress the cutaneous manifestations as quickly as is possible. The earlier therapy is instituted, the more rapid will be the response and the less steroid will be required. Initially massive doses must be ad

Not true pemphigus.

ministered, and the more extensive and serious the disease, the higher the initial doses must be. No hard and fast rules regarding dosage can be given, for each case has to be individualized. The mistake commonly made is that treatment is started with low daily dosages which are inadequate to suppress the disease. In treating a grave illness such as pemphigus, one need not be deterred by fear of the physiologic side effects, which are inevitable in those instances where very high doses are required.

As soon as a satisfactory clinical response is obtained—no new lesions appearing, the old lesions involuting, and material improvement in the patient's general condition—the daily dosage of steroid is gradually reduced to reach a maintenance level dose. The aim of treatment is to keep the patient comfortable and fairly free of eruption at the lowest possible effective dosage level. Care must be taken not to reduce the amount of daily steroid too abruptly for this may bring on a break-through. The appearance of a few new lesions does not require an increase in dosage. In the event of obvious flare-up, the amount of steroid will have to be raised again to a higher adequate level.

Various treatment schedules employing corticotropin, corticosteroids and combinations have been equally effective. For control of severe cases, the following initial daily doses are usually required:

1. Aqueous ACTH 25 to 40 I.U. administered intravenously as an 8-hour infusion.
2. Cortisone 400 to 600 mg. orally.
3. Prednisone 80 to 120 mg. orally.

Some patients may need higher doses.

The drugs of choice at present are prednisone and triamcinolone. These are corticosteroid compounds which, in general, present less hazard from side effects. Prednisone, in starting doses of 80 to 120 mg. daily, will have prompt suppressive effects. As soon as improvement is noted, the daily dosage can be gradually reduced by decrements of 2.5 to 5 mg. once or twice weekly. The maintenance dose may vary, but usually will be found to range between 20 and 30 mg. daily. In some few patients, the maintenance level may be even further lowered. One must

cautiously attempt reduction to the lowest possible dosage directed toward a gradual termination of treatment, if possible.

Triamcinolone, the most recent cortisone derivative, has not yet been adequately evaluated for its effectiveness in pemphigus. Preliminary reports [9] and observations indicate that it produces no sodium and water retention, and that its antiinflammatory effect upon cutaneous lesions is much higher than that of other corticosteroids. In dosages two-thirds to three-fourths that of prednisone, triamcinolone produces comparable therapeutic effects in many dermatoses.

Although the author's experience with triamcinolone treatment of pemphigus has thus far been limited, results achieved in some few patients indicate that triamcinolone affords definite advantages. Patients have demonstrated prompt response to 50 to 80 mg daily and have been maintained on as little as 8 to 12 mg. Side effects have been less than those noted with prednisone therapy although this may be solely on the basis of lower dosage requirements. However the same serious side reactions that occur with prednisone administration have been encountered from comparable high dosages of triamcinolone.

Additional Measures. The patient with pemphigus requires close medical supervision, nursing care, and supportive treatment. Complicating systemic or local infection, anemia, protein depletion, electrolyte imbalance, and side effects from therapy must be watched for and appropriate preventive or corrective measures taken. With steroid treatment, bacterial infections of the skin are not uncommon and usually require systemic antibiotic treatment. Antibiotics should not, however be given prophylactically but should be reserved for manifest infection.

The use of steroids has reduced considerably the need for local therapy which in the past was a major nursing problem. A daily tub bath with plain water or with potassium permanganate added, may be given. If tolerated, the use of a hexachlorophene soap will aid in cleansing and in reducing odor After drying of the skin, sterile talc may be dusted over the lesions. On vegetating pustular lesions, the application of Vioform or Chloromycetin cream is of definite value.

Costello et al. [10] found that pemphigus vulgaris and pemphigoid responded best to corticosteroid therapy: pemphigus vegetans and pemphigus erythematosus, not as well. The least favorable response was that of pemphigus foliaceous. They stated that pemphigus foliaceous was benefited by administration of antimalarial drugs, particularly quinacrine (Atabrine) hydrochloride. Reznick et al. [11] felt that in early pemphigus foliaceous, if the disease was localized and mild treatment could be withheld. In pemphigus erythematosus, the lesions may be few in number and often remain localized for variable periods of time. Remissions are common. Under these circumstances, it probably is wise to delay steroid treatment until there is evidence of spreading. Local treatment with Vioform-hydrocortisone cream is sometimes helpful.

With current steroid therapy the patient with pemphigus can be kept alive to enjoy a fairly normal life for an indefinite period of time. The problem is mainly one of complications from therapy. Perhaps, in the near future, as new safer steroids are developed, treatment may become less hazardous. There is no doubt that symptomatic treatment of this nature is far from ideal, but until such time that the cause of pemphigus is uncovered, this form of therapy is the best we can offer.

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Edward L. Laden

20

CUTANEOUS INFECTIONS CAUSED BY STAPHYLOCOCCI AND STREPTOCOCCI

It is now generally accepted that in the common bacterial infections of the skin, known as the pyodermas, coagulase positive, hemolytic *Staphylococcus aureus* and beta hemolytic streptococci are the principal pathogenic organisms. However in order to evaluate cultures taken from these and other skin lesions, one must have some familiarity with the bacterial flora of the skin in health and disease.

Studies conducted over the past twenty five years have demonstrated that it is impossible to sterilize the skin of all its bacteria. As a result the concept of resident and transient organisms has been established. This view states that a healthy skin supports a luxuriant microflora, particularly in the orifices of its hair follicles and openings of sebaceous glands Species of staphylococci make up the greater part of the aerobic flora, particularly *Micrococcus albus* and *Micrococcus epidermis*. Other organisms are varieties of corynebacterium and such anaerobic bacteria as *Propionibacterium acnes*. Certain fungi such as *Pityrosporon ovale* and *Pityrosporon orbiculare* are also resident organisms. These resident organisms are not affected by the skin s own degerming capacity

Some, in fact, depend on oleic acid and other acids present in human sebum for their survival. They are of further interest in that over the years some of them have been considered to be the causes of certain common skin diseases, such as *P. ovale* for seborrheic dermatitis and the propionibacteria for acne vulgaris. However, most authorities today are of the viewpoint that these so-called resident organisms are nonpathogens.

The transient organisms which are cultured from the skin and which may include all the known varieties contacted by man are not normally tolerated by healthy skin. In disease, however, they become more persistent inhabitants. When we study the pyodermic group of cutaneous diseases, we find that two organisms, the hemolytic, coagulase positive *S. aureus* and hemolytic streptococci are found together or separately in over 90 per cent of cases. Other organisms, such as members of the coliform group, *Proteus* and *Pseudomonas*, are less frequently found. Infections from which a pseudomonas is isolated are usually chronic and occur in the external auditory canal, the interdigital spaces of the feet, and sometimes other intertriginous sites, as well as in chronic ulcers. The other Gram-negative rods, including *Escherichia coli* and species of *Proteus* and *Alcaligenes*, may occur alone in apparently secondarily infected dermatoses but are usually found in combination with staphylococci and streptococci. There is some doubt as to whether the Gram-negative bacilli are truly pathogenic in cutaneous bacterial infection. *Pseudomonas* is, however, considered to be the most likely pathogen of the group.

The ability of normal healthy skin to rid itself of potential disease-causing organisms has been a fascinating subject and one thoroughly studied in recent years. Organisms reach the skin from external sources, but of even greater importance is the supply from the individual's own nasopharynx and gastrointestinal tract. However, within minutes to hours they disappear, failing to become established as permanent residents. For some time the acid mantle theory was the favorite explanation for this self-degerming capacity. This concept holds that the normal acidity of the skin between pH 5 and 6 provides an unsuitable

environment for most organisms. However it has been shown that many organisms which do not survive on the skin can tolerate such pHs in cultures and even that certain resident organisms are unfavorably affected by this acid state although they have no trouble with it on the skin. Today two other explanations are accepted as the major factors in this self-sterilization The first is the physical factor of desiccation. Gram-negative organisms such as *E coli* are particularly susceptible to this factor and disappear about as rapidly when placed on an inanimate dry surface such as glass as when put on the skin. Conversely moisture such as is found in an exudate allows them to survive. Hemolytic staphylococci and hemolytic streptococci are also sensitive to this factor although to a lesser degree than *E coli*. The other important agents bringing about destruction of organisms are the fatty acids present in the surface lipids. The unsaturated fatty acid oleic acid is apparently particularly effective against streptococci. Such fatty acids are inactivated by serum and exudate also allowing these organisms to survive It is readily apparent that skin which is no longer intact quickly becomes a hospitable site for the survival of the transient pathogenic bacteria. Thus cultures from a weeping dermatitis, eroded insect bites, second degree burns, and numerous other skin lesions in which the surface integrity is no longer intact can and do show large numbers of pathogenic organisms. The problem of evaluating the role played by these organisms in the particular condition under study is very difficult. Obviously the presence of these organisms cannot by itself be accepted as evidence of infection. In order to help solve this problem, Pillsbury and Kligman have suggested the following procedure Smears are made from the surface of skin lesions and stained for cells and bacteria. If polymorphonuclear leukocytes are found in large numbers, and particularly if these cells contain engulfed cocci, they interpret this to mean that the body is reacting to the organisms which in turn are behaving as pathogens. At the present time this suggested test has not received wide acceptance and has not been well correlated with other findings to make it a routine procedure. The situation today therefore, is that the subjective judgment of the

clinician determines what is accepted as secondary infection. Unfortunately antibacterial treatment approached in this manner is often disappointing.

ANTIBIOTICS

For several years after the introduction of penicillin and other antibiotics, it appeared that the treatment of many bacteria-caused diseases might become a relatively simple and routine procedure. With the success of these agents, there was undoubtedly a general decline in the use of such diagnostic procedures as bacterial cultures and identification of responsible organisms. This situation is, however now undergoing a significant change. The introduction of many new antibiotics, the complications resulting from the use of antibiotics, and the emergence of resistant strains of bacteria have made it imperative that the practitioner become familiar with all these drugs and their use in particular conditions. The following brief review of the antibiotics, now most widely used, is directed toward their employment in cutaneous infections caused by staphylococci and streptococci.

Penicillin. This drug is in many ways the ideal antibiotic. It has potent antibacterial activity is of negligible toxicity and is of comparatively low cost Its spectrum of activity is narrower than that of many of the antibiotics developed at a later date but this property may be inseparable from its low toxicity It is probably the most effective agent against the Gram-positive cocci, and although many strains of penicillin resistant staphylococci now exist, particularly in hospital environments, this problem of antibiotic-resistant bacteria is common to all antibiotics. With the exception of the staphylococci, no other organisms have been shown to develop a significant degree of in vivo resistance to it. The big disadvantage of the drug is its relatively high allergy-producing capacity which is estimated to be about 10 per cent when the drug is used systemically Nevertheless, penicillin is still considered to be the systemic drug of choice for acute staphylococcic and streptococcic cutaneous infections.

The most commonly employed forms for systemic use are:

1. Crystalline benzyl penicillin in aqueous solution administered intramuscularly This form has a total duration of therapeutic plasma concentration of only 3 hours, and its use is, therefore, primarily in the hospital In an acute erysipelas where a rapid antibacterial effect may be needed, this form of penicillin is sometimes indicated. Also where the intent is to give very large doses in order to achieve a high level of plasma concentration in an infection caused by an organism resistant to the usual concentrations, this form of penicillin has value.

2. Procaine penicillin with sodium carboxymethylcellulose prepared aqueous suspension, 300,000 I.U administered intramuscularly Total duration of therapeutic plasma concentration is around 24 hours.

3. Procaine penicillin with aluminum monostearate in oil. Total duration of therapeutic plasma concentration is 48 to 96 hours.

4. Benzathine penicillin (N,N -dibenzylethylenediamine dipenicillin G) Total duration of therapeutic blood concentration is 10 days with 600 000 I.U intramuscularly

5. Penicillin, buffered, oral tablets—200,000 I.U tablets. Total duration of therapeutic plasma concentration is 3 hours.

Penicillin is also available for local use as ointments, nose drops, dusting powders, and troches. This local use particularly on the skin is now to be discouraged. The possibility of contact sensitization is relatively high, around 5 per cent. Other agents, equally effective in topical use and with far less sensitization capacity are now available. Such a sensitization may prevent the individual from having the future systemic use of this drug.

Streptomycin. Although effective against Gram positive as well as Gram negative organisms, this drug is not often used today in the treatment of pyodermas. The development of the broad spectrum antibiotics has diminished its need in these conditions. Also its value in the treatment of tuberculosis and certain urinary infections due to Gram-negative organisms makes it preferable to reserve it for these latter conditions. The drug must be given by parenteral route, which at times is a disadvantage. The principal toxic effect, which is on the VIIIth nerve and vestibular appa

ratus, is, of course, serious. Streptomycin should not be used topically It, too, has a relatively high sensitizing capacity in this form.

The Tetracyclines. The three drugs that belong to this group are chlortetracycline (Aureomycin) oxytetracycline (Terramycin) and tetracycline (Tetracyn, Achromycin, Steclin, Polycycline) They are chemically related, all having the same basic tetracycline structure. They are similar in therapeutic effectiveness and have similar toxic reactions. They are effective against both Gram-negative and Gram-positive bacteria, thus acting not only against staphylococci and streptococci, but also against other organisms which may be present in a cutaneous infection. They are administered primarily as oral medication although available in parenteral form. They are absorbed within 2 to 4 hours, and effective therapeutic concentrations are from 6 to 8 hours. Their principal toxic effect is the production of gastrointestinal and genitourinary disorders (nausea vomiting, diarrhea, stomatitis, vaginitis, and proctitis)

Allergy to the systemic use of these drugs is not as great as with penicillin. This relatively low sensitizing index also applies to their topical use. They are of value particularly in chronic bacterial cutaneous infection, in infections caused by organisms resistant to penicillin, and in patients allergic to penicillin. They are effective locally and may be the antibiotic of choice, depending on the results of cultures and studies to determine antibiotic susceptibility

Chloramphenicol. The range of activity of this drug is about the same as the tetracycline members. However because of its possible toxic effect on the hematopoietic system, it is not frequently used in the treatment of cutaneous infection. Topically it does not cause a high degree of sensitization and may be the drug of choice depending on the organisms isolated.

The Erythromycin Group. Since the introduction of erythromycin, other antibiotics having a similar antibacterial spectrum and exhibiting cross resistance with it have been encountered. Thus far attempts to exploit such erythromycin-like agents have been made with only three of them. The first of these carbomycin

(Magnamycin) was found to have so little clinical activity as compared with erythromycin or other available agents that its use has been almost completely abandoned. Two other new antibiotics have become available more recently oleandomycin in this country and spiramycin in France. Both are active in vitro over the same range of bacterial spectrum as erythromycin but are generally less active against most species and strains. Both agents as well as erythromycin and carbomycin show marked or complete cross resistance to strains that are made highly resistant to any one of them in vitro. However strains of staphylococci freshly isolated from patients or carriers and shown to be resistant to one have varied markedly in their susceptibility to one or more of the others.

The antibiotic spectrums of erythromycin and related drugs contain some of the properties of penicillin on the one hand and the tetracyclines on the other They are effective drugs systemically and topically against the pyodermas with erythromycin being the most effective member of the group. They show a low degree of cross resistance with penicillin and antibiotics outside their group. Sometimes they may be the only agents capable of controlling certain resistant infections.

Bacitracin. The antibacterial spectrum of this drug closely resembles that of penicillin. It inhibits aerobic and anaerobic Gram-positive bacteria but fails to inhibit most Gram-negative species in doses that are clinically practical. When given systemically it is administered intramuscularly in doses of 10 000 to 20,000 I U every 6 hours. However it is infrequently given in this form because of its toxic effect on the kidney Topically ointments containing 500 units of bacitracin per gram are very effective against many pyodermic infections.

Tyrothricin. This is one of the few antibiotics developed from a soil bacillus, the particular organism being *Bacillus brevis* It is effective mainly against Gram-positive cocci and is not suitable for systemic use because of its hemolytic action. The drug has been used extensively in wet dressings and topical ointments, although more recently other more effective antibiotics appear to be replacing it.

Neomycin. This drug displays activity against both Gram-positive, acid fast, and Gram-negative bacteria. It has many similarities to streptomycin and on systemic use may cause slight to severe deafness as well as transient renal irritation Its principal use is in the topical treatment of pyogenic infections, for which it is available in ointments containing 5 mg of neomycin per gram. It is also effective against *Proteus* and *Pseudomonas* organisms. Neomycin is the only broad-spectrum antibiotic which is stable in aqueous solution. It can be prescribed, therefore, in aqueous lotions as well as compresses, usually being in the concentration of 3 to 5 mg per milliliter

Polymyxin. This is a product of another soil inhabiting bacillus. It is very effective against *Pseudomonas aeruginosa* and its incorporation in many antibiotic ointments is for the purpose of including this property Its systemic use is limited because of its moderate toxicity on the renal and central nervous system.

Novobiocin (Albamycin) This antibiotic has been in use for clinical purposes in recent months. In vitro studies reveal it to be effective against 95 per cent of strains of coagulase-positive *S aureus* In these studies, no cross resistance with penicillin or erythromycin was demonstrated. On clinical use a rather high occurrence of skin eruptions has been noted. There have also been reports of leukopenia developing on continued use of the drug. Nevertheless, it is too early to evaluate the future use of this drug.

Combined Antibiotic Therapy

The increase in the number of antibiotic-resistant staphylococci and other organisms encountered in clinical practice has led to use of antibiotics in combination. Studies of combinations such as chloramphenicol and oxytetracycline or oleandomycin and tetracycline have been made in vitro and in vivo It has been claimed that a synergistic effect occurs, in that such combinations are distinctly more effective than when the agents are used alone. This has led to the introduction of Signemycin, which is a 2 1 mixture of tetracycline and oleandomycin. In this combination each drug is present in quantities less than if they were to be

used alone. This approach to the problem has been severely attacked by others. They claim that they have been unable to confirm a synergistic effect of such combinations. It is stated that such combinations represent a return to the shotgun era of the past.

Antibiotic combinations for topical therapy have received much more unanimous support and at the present time are probably more widely used than single antibiotics. This is particularly true in regard to the combinations of neomycin and bacitracin, and neomycin, bacitracin, and polymyxin. It is claimed that neomycin, which has quite a broad spectrum including Gram-positive cocci and Gram-negative bacilli, is not the treatment of choice for hemolytic streptococci. Bacitracin, which is effective against Gram positive cocci, is not effective against the Gram negative organisms. Polymyxin B is considered the most effective against *Pseudomonas* but has no effect on Gram positive cocci. *Although such combinations may be associated with a slightly* higher incidence of sensitivity reactions than one of the agents alone, the fact remains that the actual incidence is still very low

It should be pointed out that the reason most dermatologists prefer neomycin and bacitracin to other broad spectrum anti biotics for topical use is that these drugs are rarely used for systemic therapy If allergic sensitivity should develop from topical use of an antibiotic, it is preferable that the agent be one which will not be needed at a later time for systemic therapy Also, antibiotic resistant strains can develop from topical therapy It is preferable that such strains be resistant to an agent which is not likely to be used systemically

Although the present practice is to use such combinations in topical therapy it should be emphasized that, in chronic infec tions or where satisfactory improvement does not take place in acute infections within 5 to 7 days, cultures and antibiotic susceptibility be determined Otherwise, further antibiotic ther apy cannot be intelligently continued

Combined Cortisone and Antibiotic Therapy

In general, cortisone is not used with antibiotics in the systemic treatment of cutaneous infections. There may however be exceptions, such as in pyoderma gangrenosum and other similar necrotizing diseases where a hyperergic reaction is a possible mechanism. There are reports where cortisone appeared to be essential for the healing of such lesions.

The topical use of hydrocortisone with antibiotics has been widely accepted. In a sense this is a remedy designed more for the treatment of dermatitis where bacteria are considered to be playing a secondary rather than a primary role. It is a fact that there are cases where it is impossible on clinical grounds to decide whether infection is primary secondary or even operative. This is particularly true of certain exudative lesions. In the past, the application of such antibacterial agents as ammoniated mercury has led to catastrophic results with severe exacerbation of the eruption. A combination of neomycin and hydrocortisone is a distinct advance in the management of such eruptions. Nevertheless, one should not ignore the fact that such combinations are a shotgun type of remedy There is no evidence that the combination is more effective than either alone when specifically indicated. The success of such combinations encourages the pharmaceutical houses to introduce more and more combinations including drugs such as tars and Vioform as well as the antibiotics and hydrocortisones. Such combinations are more sensitizing, more expensive, and less scientific. Probably the worst effect of all is that they discourage intelligent evaluation of the disease by the practitioner by trying to provide an agent which will work against any inflammatory eruption

Antibiotic Susceptibility Tests

It has been found that clinical response of an infection to antibiotic therapy is in general in good agreement with the results obtained by in vitro tests. The use of such tests by most laboratories has now become routine the most commonly used being the paper disk method. *Staphylococcus aureus*, one of the

important organisms in cutaneous infection, is commonly found as strains resistant to one or several of the various antibiotics. *Streptococcus pyogenes* on the other hand, rarely exhibits antibiotic resistance

Cross Resistance to Antibiotics

It has been observed that an organism may on exposure to an antibiotic develop strains resistant not only to this agent but also to other antibiotics to which it may not have been exposed. This has been called cross resistance. In general, the development of cross resistance has been limited largely to chemically related antibiotics. Among the tetracycline drugs this has occurred rather frequently The same can be shown for erythromycin and its related compounds carbomycin, oleandomycin, and spiramycin. Cross resistance between the tetracyclines and chloramphenicol appears to vary with the bacterial species, some developing significant resistance while others show none at all. No cross resistance between tetracycline and penicillin or tetracycline and streptomycin has been noted. Streptomycin and neomycin, despite certain important similarities, do not seem to exhibit cross resistance with each other Nor does the erythromycin group show cross resistance with penicillin, the tetracyclines and chloramphenicol.

Complications of Antibiotic Therapy

Dermatologic. The most common skin complication of antibiotic therapy is urticaria. This may be mild or severe. It may last only a few days or go on for a few weeks, even eventually into a chronic urticaria. It may occur as part of a serum sickness reaction with joint pain and elevated temperature Another skin complication is a so-called allergic toxic eruption. This may vary from a morbilliform, macular erythema to a bullous erythema multiforme. True dermatitis is another complication of antibiotic therapy With penicillin particularly it may begin on the feet, hands, and groin as a dermatophytid type of reaction. Exfoliative dermatitis has been known to develop from this as well as from the toxic type of eruption. Allergic contact dermatitis has been

described with all the antibiotics. It is sufficiently common with penicillin and streptomycin to preclude their use in topical therapy. Stomatitis with a reddened, inflamed mucosa and tongue has resulted from the broad-spectrum antibiotics. The use of troches and lozenges has resulted in the development of hairy tongue, a peculiar condition in which long brown to black pseudopapillae are seen on the surface of the tongue.

Gastrointestinal. Nausea, diarrhea, and pruritus ani are not infrequent complications of broad-spectrum antibiotic therapy. The latter two complaints have been attributed particularly to a reduction in the normal bacterial growth of the intestine and a corresponding increase in the number of *Candida albicans*. In order to control this, Mycostatin, an antifungal agent, has been combined with the broad-spectrum antibiotics. The introduction of tetracycline has brought about a definite decrease in these gastrointestinal complaints, which in turn casts some doubt on the role of *Candida*.

Pulmonary. Anaphylactic shock resulting from allergy to penicillin is probably the most dreaded complication of antibiotic therapy. It is estimated that several hundred such reactions have occurred, resulting in a large number of deaths. The classical scratch or intradermal test for detecting allergic sensitization is of value in the prevention of this complication. It should be routine in patients with a history of possible allergy to penicillin and patients with asthmatic backgrounds.

Superinfection of the lungs with such organisms as *Candida*, *Proteus*, *Klebsiella*, and *Pseudomonas* is becoming more common in patients who are receiving antibiotics. Steroid therapy appears to foster the growth of these organisms. Since these organisms are usually resistant to the more commonly employed antibiotics, a real therapeutic problem may result.

THERAPY OF SPECIFIC BACTERIAL DISEASES

The classification of pyodermas into primary and secondary types is of value in a discussion of these disorders. In general, in the primary pyodermas, there is no preexisting dermatosis. The predominant organisms found are the coagulase positive

hemolytic staphylococcus and beta hemolytic streptococcus. Elimination or control of these organisms by drug therapy will usually lead to a disappearance of the condition. In the secondary pyodermas, some other dermatosis such as atopic dermatitis or seborrheic dermatitis has existed and the infection is therefore superimposed. The coagulase-positive staphylococci and beta hemolytic streptococci are the most common invaders, but Gram-negative organisms (*Proteus Pseudomonas, E. coli*) often are found. In certain locations, such as the external ear *Pseudomonas* is believed by some to produce true secondary infection, although the actual role of these Gram-negative organisms in cutaneous infection is still obscure. Control of these organisms by drug therapy may contribute but rarely by itself leads to disappearance of the disease.

CLASSIFICATION OF THE PYODERMAS

1. Primary type
   - *a.* Impetigo
   - *b.* Folliculitis
   - *c.* Furuncles
   - *d.* Erysipelas
   - *e.* Sweat gland infections
2. Secondary type
   - *a.* Infectious eczematoid dermatitis
   - *b.* Otitis externa
   - *c.* Nonspecific secondary infections

Impetigo. Treatment of the various forms of impetigo is usually direct, simple, and effective. Difficulties arise where diagnosis has not been correct or where certain basic principles of skin care are not observed.

The recognition of the common form of impetigo, the so-called impetigo vulgaris, should not be a problem. The infection is very superficial, occurring just under the horny layer and involving the upper portion of the epidermis. The very superficial denudation of the upper epidermis leads to early oozing of serum and its coagulation to form serous crusts. On removal of such a crust, *the underlying lesion consists of slight redness with no palpable infiltration.* The lesions grow rapidly at first but then

stop, rarely exceeding the size of 1 to 2 cm. The condition is infectious to the patient, and multiple lesions developing fairly rapidly within a few days are the rule. Rarely does it remain localized to one small area but moves out over the face. It may even appear on the trunk or extremities. The most commonly encountered difficulty in recognizing the condition arises in confusing it with certain exudative forms of dermatitis. It is common for contact dermatitis and atopic dermatitis to involve the face. Both conditions are often patchy and may be exudative, developing serous crusting. Although itching is usually severe, impetigo also may cause moderate itching. Familiarity with these conditions will usually lead to a correct diagnosis, but it is not uncommon for a mistake to be made. Usually the mistake lies in confusing dermatitis with impetigo. In the past this not infrequently has led to serious difficulties, since some of the antibacterial agents such as ammoniated mercury ointment were not always well tolerated by a severely inflamed dermatitis. The topical antibiotic agents in use today rarely lead to such flare-ups, and combinations such as neomycin and hydrocortisone are helpful in being effective against both infection and dermatitis. The other source of difficulty in the treatment of impetigo lies in failing to recognize that a skin which is being irritated or sensitized will not heal regardless of how effectively bacteria are being destroyed. Thus the management of impetigo does not call for too vigorous cleaning with soap and water. Soap and water may be helpful but unless patients are instructed in its correct use, it is not uncommon to see irritation result. Gentle compressing is often a better solution, since it removes crust and other exudative debris without harming the skin. Blisters and pustules are best opened by trimming away the top of the lesion with a small scissors. The agent to be used is then gently applied to the lesion without vigorous rubbing. Dressings are avoided, but the antibacterial agent is applied frequently, as often as every 2 to 3 hours if possible.

The ointments of choice at the present time for the treatment of simple impetigo vulgaris are neomycin, bacitracin, or combinations of neomycin and bacitracin with or without polymyxin.

The tetracyclines, chloramphenicol, and erythromycin are all satisfactory for topical treatment of impetigo with the one disadvantage that they are also systemic agents. Penicillin and streptomycin are not recommended for topical use because of their relatively high sensitizing potential as well as their use in systemic therapy. Combinations of hydrocortisone and antibiotic are not recommended for topical treatment of impetigo unless a differential diagnosis from dermatitis cannot be made. Except for infants and debilitated adults, systemic therapy of impetigo is rarely indicated. Penicillin is the agent of choice, although in a hospital where the incidence of penicillin-resistant staphylococcus may run as high as 75 per cent, the other antibiotics may be indicated. The choice of antibiotic may then depend on the antibiotic susceptibility tests.

Other less common forms of impetigo such as bullous impetigo are occasionally encountered. The thin-walled blister, usually partially collapsed and filled with purulent secretion, is characteristic. Local treatment is usually all that is necessary, although since this form is more common in infants and debilitated adults and may also become generalized in an individual with lowered resistance, systemic therapy may be necessary. What was formerly termed *Pemphigus neonatorum* is an extensive form of infantile bullous impetigo. Prior to the antibiotic era, it was one of the most feared of infantile infections.

Impetigo in certain locations, particularly hairy areas, requires special attention. Impetigo of the scalp is occasionally seen and should always arouse suspicion of the concomitant presence of pediculosis capitis. The latter must be eliminated with the application of benzene hexachloride (Kwell ointment) in order for the impetigo not to recur. The removal of crusts and scales is difficult. Compressing of the scalp is usually not feasible. A good procedure is to begin treatment first with an oil cap to soften crusts, followed by gentle soap and water shampoo and then application of the topical ointment.

Impetigo of the beard area in men raises the problem of whether to shave or not. There is a risk of inoculating microorganisms with the razor. However, in general, it is much cleaner

and bactericidal to allow daily shaving. Matted hair pus, and crusts form a culture chamber and a barrier to proper application of topical medicaments It is a good routine to apply the antibacterial ointment before and after shaving. Use of a fresh, sharp razor blade is preferable to an electric razor which removes the hair with more difficulty

Impetigo occurring in newborn infants in a hospital was a feared calamity prior to the antibiotic era. Much of the hygienic procedure practiced in the hospital nursery is directed toward the prevention of this disease. A recent report of such an occurrence is of interest. The organisms were coagulase-positive staphylococci resistant to penicillin, streptomycin, and tetracycline An incidence of staphylococcic infection occurred in early life in 22 per cent of infants in a large general hospital. The infection included five breast abscesses of infants, one of which was fatal. An epidemiologic study revealed that the source of the infection was neither the mother nor the hospital personnel but rather infants who were subclinically infected with *S aureus* In other words, the newborn infants brought into the nursery where other infants had infection quickly acquired the organism, either in their nose and throat or on their skin They then in turn became responsible for seeding large numbers of the organisms onto their sheets and bedclothes. When the nursing staff changed the sheets, organisms were disseminated into the air and settled down onto the other infants. Aerial transmission thus appeared to play an important role in spread of infection from infant to infant. It is apparent from such a report that pyoderma in an obstetrical unit can again, in spite of antibiotics, become a serious problem.

Ecthyma. This cutaneous infection, in contrast to impetigo, is a deep, destructive process leading to ulceration and healing always with scar formation. It is not autoinoculable and contagious, although multiple lesions may occur It is rare that ecthyma occurs without other factors being of importance causatively These factors may be environmental, such as the climatic factors of the tropics, where heat and perspiration seem to contribute to a greater occurrence of this disease. They may be

lack of hygiene such as occurs in a soldier during combat or an alcoholic on Skid Row. They are often the result of some deficiency such as poor nutrition in an alcoholic or a chronically ill person. Systemic disease such as diabetes and lymphomas predispose to ecthyma. Local vascular factors both arterial and venous may be the underlying cause. Other antecedent skin conditions such as pediculosis, scabies, and occasionally eczema may be the starting factors for ecthyma. Certain of the exanthems, vaccinia, variola, and varicella have at times led to its development. In general, the presence of ecthymatous lesions must be cause for further consideration of underlying predisposing factors.

Ecthyma most commonly starts on the legs. The earliest lesion may be described as an insect bite, a scratch, or a black and blue mark from a contusion. The area then becomes red, tender or perhaps hemorrhagic and begins to break down. When seen by the examining physician, an irregular lesion covered by a purulent crust and surrounded by a zone of bright erythema is noted. On removal of the crust, an ulcer with a dirty base covered with a purulent or hemorrhagic exudate is noted.

The treatment of ecthyma calls for treatment of the skin lesion plus any of the various contributing factors. Warm compresses usually of normal saline repeated two to three times daily are indicated to clean the area in a gentle fashion of crusts and exudate. If the patient can be put to bed, elevation of the leg, compressing, and keeping the area otherwise dry may be sufficient for healing. Topical antibiotic ointments, particularly those with a greaseless base, may be used, but one must be on the lookout for maceration. If maceration does occur, parenteral antibiotic therapy rather than topical antibiotic is indicated. Often the patient can be kept ambulatory by using compresses day and night, gauze dressing with topical antibiotic, and an elastic bandage while he is up and around. Adding to this one of the systemic antibiotics, one may expect a very satisfactory result. These cases usually are best handled from the antibiotic standpoint by culturing them early and doing antibiotic susceptibility tests. Hemolytic streptococcus may be the important organ

ism, and fortunately this organism is usually susceptible to the action of the antibiotic. It should also be emphasized that urinalysis, blood sugar determination, and certainly a blood count and differential blood smear should be a routine procedure in the management of ecthyma.

Gangrene of the Skin, Ecthyma Gangrenosum. A number of conditions have been described which bear a relationship to ecthyma and which can be discussed in connection with that disease. Various authors have described these conditions under different names, and it is most confusing to classify them. The best known is so-called pyoderma gangrenosum.

Pyoderma Gangrenosum. This disease has been most commonly associated with the presence of ulcerative colitis, although it may occur in other chronic and debilitating diseases. The lesions are usually multiple ecthymatous ulcers which show a frightening tendency to advance despite treatment. The borders of the ulcers are usually edematous, and occasionally even blisters and pustules are present. There may be a distinct purple color and round this a zone of erythema. Not uncommonly only part of the border may show signs of progression. The general shape of the lesion is thus often irregular even polycyclic or serpiginous. The base of the lesion is the typical dirty purulent base of an ecthy matous lesion. Such lesions may start following intestinal surgery in the operative site or they may occur without any particular preexisting wound.

Cultures from these wounds usually show a mixed growth with staphylococci and streptococci being the most common organisms isolated. The Gram-negative bacilli are often isolated.

Cultures and antibiotic susceptibility tests are certainly indicated for these lesions. Vigorous antibiotic therapy both local and systemic is imperative. Despite the most intelligent use of these drugs, response to such therapy may be very poor In these cases a determination of the gamma globulin level is occasionally rewarding. Certainly the absence of gamma globulin or a low gamma globulin level calls for administration of this agent. Some have advocated the concomitant use of gamma globulin and antibiotics regardless of the laboratory determination. There have

also been reports of excellent response to cortisone therapy combined with an antibiotic where the latter by itself was unsuccessful. Cases showing progressive ecthymatous lesions which, despite the use of antibiotic susceptibility tests and evidence of susceptible organisms, did not respond to antibiotic therapy healed when cortisone was administered in large doses along with antibiotic. Certainly there is less occasion today to resort to the former drastic procedure of wide surgical excision of such a lesion.

Dermatitis Gangrenosum. This condition, also known under the names of dermatitis gangrenosum infantum infectious multiple gangrene of the skin, and gangrenous impetigo is a serious form of ecthyma which is usually superimposed upon some pre-existing cutaneous lesion in an individual whose resistance has been lowered by ill health. Such lesions were at one time seen in poorly nourished infants following attacks of varicella and vaccinia. The lesions are usually multiple They often show a large amount of hemorrhage giving them a red and then blue color The area may turn black and slough, leaving an ulcer covered by a necrotic crust. The bacterial organisms found here are most probably secondary invaders. It is also likely that this condition may represent a severe allergic reaction of the Schwartzman or Arthus variety As in the preceding condition, therapy calls for attention not only to the organisms but also to such factors as gamma globulin. Cortisone and other steroids may be of considerable value because of their ability to suppress allergic reactions.

Folliculitis Classification of folliculitis is difficult. Division into superficial and deep varieties seems of little significance. Causative factors are most important and should be carefully searched for in each case of folliculitis. Bacteria are rarely the responsible agents by themselves

Bockhart's impetigo so-called, is the simplest form of folliculitis. The lesions are superficial and consist of small thin-walled pustules, perforated in their centers by a hair Staphylococci are usually *isolated from these lesions.* They occur most commonly in areas of maceration such as under tape dressings or intertriginous

sites as in the axillary or crural region. They may be near an area of a draining infected sinus or wound. They are easily cleared by a combination of a topical antibiotic ointment in a greaseless base and elimination of excessive moisture and maceration. The use of neomycin which is water soluble, in a simple shake lotion may at times be applicable, although this is not practical in hairy areas.

At times this type of folliculitis may become more chronic and recurrent. Such lesions occasionally occur in the scalp and not infrequently over the skin of the buttocks and posterior thighs. In both regions it is important to clear any preexisting dermatitis with its associated pruritus. Pruritus and chronic scratching may cause repeated folliculitis. It may also be important to correct a situation where clothing rubs against the skin such as a suspensory in the scrotal and inguinal areas. Cleanliness is of utmost importance in the elimination of chronic folliculitis, and the use of soaps containing hexachlorophene may be helpful. Systemic antibiotics are usually not indicated but at times may be worthy of trial. Where it is effective, it is worth continuing for 2 to 3 weeks after the eruption clears to prevent recurrence. In general, the treatment of chronic folliculitis involves restoring the skin to its normal state of resistance as much as eliminating the infectious agents.

Sycosis Vulgaris. This eruption is considered to be a chronic folliculitis of the bearded area. Although staphylococci and streptococci are found in the lesions, the factors that cause this condition to be so persistent are still not known. The lesions are follicular pustules pierced by hairs. Considerable swelling may at times produce a granulomatous appearance. The hairs are usually not easily detached, nor does this condition lead to permanent loss of hair or scarring.

In treatment the control of bacteria is essential. Cultures and antibiotic susceptibility studies are worthwhile, particularly if there has been much past treatment with antibiotics. Topical antibiotic ointment and oral parenteral therapy will then be on a more rational basis. Warm compresses two or three times daily for 15 to 30 minutes may be helpful.

Shaving should be done one time daily. A sharp safety razor is preferred to an electric razor. It is important to instruct the patient in the technique of shaving. The blade should be moved only with the direction of hair growth rather than against the grain to cause the least irritation. Application of the antibiotic ointment prior to the shaving cream may reduce danger of infection and also protect the skin from irritation. In resistant cases, manual epilation of hairs from areas of involvement may help a great deal. The hairs appear to be acting as foreign bodies in these lesions with healing not taking place until they are removed.

It is a common mistake to confuse dermatitis in the bearded area with sycosis vulgaris. This is due to the fact that inflammation in a skin where there are a large number of hair follicles results in swelling of the follicular orifices and production of follicular papules. In general, however, the involved areas are ill-defined and not discrete follicular lesions as in sycosis. In men who irritate their skin from shaving too often, too closely, or with a dull blade, so-called ostio folliculitis results. Response to bland antidermatitis treatment usually clears such lesions rapidly.

Special Forms of Folliculitis. Folliculitis occurring in people exposed to such chemicals as chlorine, tars, pitches, certain chlorinated waxes, machine oils, and cutting oils is seen, these exposures usually being occupational in nature. Bacteria are not primary in these but may act as secondary or superimposed factors. Such lesions often show features of acne with comedos, cyst formation, and indurated nodules. They are most commonly seen on the extremities, where exposure to clothing saturated with the chemical has been the greatest. These lesions at times are very slow to recede, even when no further exposure to the causative agent is taking place. In general treatment is similar to that of acne. At times secondary infection requires treatment with antibiotics.

Furuncles and Carbuncles. A furuncle, no matter how deep, is always caused by external infection, the organisms penetrating by way of the hair follicle. The reaction of the skin, which may be quite intense, results in the production of a deep nodule

exquisitely tender which will resolve usually only after a certain amount of necrosis of tissue has occurred. The natural course of this lesion is one of self limitation, and, as in most self-limited lesions, conservatism is usually the preferred approach. It is therefore considered unnecessary and at times actually harmful to interfere surgically early in their course When the lesion is fluctuant and soft with a yellow center a nick at the apex may bring about drainage a few hours earlier than would occur spontaneously but the old fashioned cruciate incision should be a thing of the past. Hot wet compresses are of value in speeding up resolution of the lesion. Once the lesion begins to drain, it is important to cover the area with a large gauze dressing, so that the purulent drainage will be trapped before contacting other skin areas. Antibiotic ointment is usually applied over the surface of the lesion in an effort to control the bacteria present in the drainage. Although systemic antibiotic is probably not necessary in the treatment of a single furuncle, it should be routinely used in lesions about the nose and upper lip to eliminate danger of intracranial extension, in large furuncles and furuncles of the external ear canal. In general one cannot be unaware that a single furuncle of the skin has at times been responsible for glomerulonephritis, staphylococcus abscesses of internal organs such as the kidney and even a staphylococcus septicemia.

The treatment of recurrent furunculosis calls for a redoubling of efforts to eliminate all the contributing factors. First of all, one must not forget that certain systemic diseases such as dia betes, lymphomas, and other blood disorders may predispose one to repeated pyodermas including furuncles. Working conditions of excessive heat and lowered hygiene may be contributing factors. The question of whether excessive intake of carbohydrates may contribute is in dispute although earlier work by Urbach suggested that this may be a factor It certainly is important to correct obesity and where a patient s diet may be weighted too heavily in favor of carbohydrates, a reduction in this is worth trying.

Continued efforts to reduce the bacterial count of the skin are valuable. Active lesions must be cared for as described under

treatment of the single lesion. Soaps containing hexachlorophene should be used daily in the shower Excessive perspiration should be avoided, and clothing should be cleaned frequently Although *it is impossible to sterilize the atmosphere, staphylococci can live* for long periods on clothing and bedcovers.

Continued systemic antibiotic therapy usually with the oral antibiotics, may be of value in the treatment of furunculosis, although in general they are used only in the presence of active lesions. Nonspecific measures such as general ultraviolet radiation may contribute to an increased resistance of the skin

Carbuncles can be thought of as a combination of furuncles and are characterized by multiple areas of softening and drainage Their management is in general the same as that of furuncles. Systemic antibiotics are practically always indicated, but radical surgical measures should be avoided.

Erysipelas. This cutaneous infection is a cellulitis caused by a beta hemolytic streptococcus. The involvement is relatively superficial and is characterized by a rapidly spreading red edematous plaque The border is usually fairly sharp and can be observed to spread peripherally The favorite sites are the face and scalp, but involvement of the extremities is not uncommon. There is usually evidence of systemic reaction such as elevated temperature a sense of malaise and ill being.

Treatment is the administration of systemic antibiotics. Penicillin is usually given intramuscularly and here aqueous penicillin may be of value early in the course of treatment. If allergy exists to penicillin, the other antibiotics such as the tetracyclines and erythromycin are effective. The causative organism is not one to show resistance to antibiotics.

Occasionally certain individuals have repeated attacks of *erysipelas occurring even as often as every few months.* The complication to be feared from this is permanent damage to the lymphatics with a resulting persistent swelling of the affected part The latter is referred to as elephantiasis nostras, or solid edema. It has been known to affect a lip a nose, or at times one or both lower extremities. To prevent such repeated infection is therefore of real urgency This involves a search for possible

portals of entry where hemolytic streptococci may enter the tissues. Chronic areas of inflammation such as a dermatophytosis involving the interdigital spaces of the feet may provide such a portal. A chronic otitis externa may be the pathway for such infection on the face. In such individuals continued use of an antibiotic ointment on such potential portals may be of value. Continued systemic therapy is also worthwhile at times. It is important to suspect recurrent erysipelas. Sometimes in repeated attacks the individual's systemic reaction may be relatively mild, and he may not give it much notice.

Hidradenitis Suppurativa. This condition is characterized by the occurrence of deep-seated tender nodules most commonly in the axillae but occasionally in the groins and adjacent areas. The involvement is of the deep and large pilosebaceous structures and particularly the apocrine glands which abound in these areas. Although the disease may be acute and relatively short lasting, it commonly progresses into a chronically recurring, disabling disorder with production of sinus tracts, repeated exacerbation with new production of nodules and tracts. The individual lesions behave not unlike boils, although they may not always open to the outside and discharge their contents. The organisms are probably acting as secondary bacterial invaders, although their control is important. The condition may not uncommonly begin as a simple dermatitis often resulting from the use of underarm deodorants or other contact factors. In certain cases, particularly where there is evidence of certain severe forms of acne or folliculitis, one must consider that an anomaly of the pilosebaceous apparatus may preexist and thus predispose to such a condition.

Treatment involves elimination of all external irritants such as deodorants and treatment of the infection with hot compresses and systemic antibiotics. If the lesions open and drain, they are managed similarly to draining furuncles. In chronic hydradenitis, prevention of exacerbations is most difficult. X-ray therapy is often disappointing, particularly in the presence of much scarring or sinus tract formation. Cortisone internally has been useful in aborting an attack and suppressing the lesions before they can

break down. This is usually given along with systemic antibiotics. Surgical drainage with exteriorization of sinus tracts is important. The most drastic procedure of all, but sometimes necessary is complete excision of the entire area with full-thickness grafting.

TREATMENT OF THE SECONDARY PYODERMAS

Infectious Eczematoid Dermatitis. This condition has become so uncertain and confused in its definition as an entity that it would probably be a step forward if the term were abandoned. Engman originally described it as dermatitis arising on skin which was adjacent to an area of infection and which was being bathed by exudate and secretion from the infection. The infection might be an ulcer a chronically draining sinus, or even a draining middle ear infection. Since this original description, the term has been used for dermatitis such as nummular eczema, contact dermatitis, and seborrheic dermatitis where it was believed that secondary infection was of importance in causing continued activity of the underlying condition. Also, exudative *dermatitis in which autosensitization has taken place has frequently* been labeled as infectious eczematoid dermatitis. It has never been established that bacteria can cause a dermatitis, nor has a contact allergic sensitivity to a purulent exudate ever been proved. No doubt physical factors such as maceration by the exudation may play a role in making the skin more able to develop a dermatitis. In many instances infectious eczematoid dermatitis may represent a contact dermatitis due to topical medication used in treatment of the original area of infection.

The treatment of this condition consists of compresses in order to establish a clean terrain and promote the drying up of the exudate. A topical antibiotic, neomycin, or tyrothricin may be used in the compressing, although usually plain saline or a dilute boric acid solution is effective. Topical antibiotic ointment may be of aid, and the combinations of topical antibiotic and hydrocortisone may at times be indicated. In some instances, systemic antibiotics seem to bring about a more rapid and even dramatic healing of such lesions than any other therapy. Unfortunately

this is very unpredictable, and the situation where no apparent effect from the antibiotic at all can be observed is frequently the case.

Otitis Externa. In many ways this condition is an excellent illustration of the confusion that has arisen in the past over interpreting the role of the bacterial and fungal flora in causation of a dermatitis. Otitis externa is in essence a dermatitis. The changes are those of redness, edema, oozing, crusting, scaling, and even in some instances lichenification. At times the exudate may be cloudy but it is most rare to see drainage of real pus without the presence of some true infection such as a furuncle in the ear canal. The anatomical make-up of the ear canal with the difficulty of cleaning it in contrast to practically all other areas of the skin makes it a site for many organisms to thrive. Also, once the factors of moisture and maceration develop, these organisms flourish with abandon. Saprophytic fungi such as *Aspergillus Actinomyces*, and *Candida* may grow abundantly to form a cast of the canal. Their growth has impressed many observers sufficiently to attribute to these organisms the major causative role in otitis externa. This concept of otomycosis as the major form of otitis externa has held sway for years, and many excellent otologists still consider it to be a most, if not the most, important cause. In fact, however these organisms are not different from ordinary saprophytes found on diseased skin, and they have not been shown capable of causing skin infection or dermatitis.

Similar misunderstanding has arisen over the role of bacteria in otitis externa. In addition to the staphylococci and streptococci, other organisms such as coliform bacteria and species of *Pseudomonas* and *Proteus* are commonly found. *Pseudomonas aeruginosa* particularly has been found in abundance in chronic otitis externa, and there are some who feel it is the cause of this disease However although there is still a strong sentiment for accepting this organism as playing some role in the continuation of a chronic otitis externa, the available objective evidence cannot gi e these organisms more than a secondary role.

Dermatitis of the external ear canal is like dermatitis else-

where usually a manifestation of such entities as atopic dermatitis, contact dermatitis, seborrheic dermatitis, and psoriasis. Pruritus plays a major role and is often the initial symptom. Scratching or irritating the external ear canal with such instruments as a cotton applicator hairpin, matchstick, or a well tapered fingernail is practically the rule in these patients. Often they have been conditioned from early life in the insertion of some object into the ear canal to clear it of wax and debris. This local irritation is often the starting of the dermatitis Topical application of various home and drugstore remedies may further aggravate the itching and inflammation. Nervous tension may rapidly add its effect to the establishment of a continued pruritus. Sometimes the physician may continue the process by starting the patient on a routine of treatment of the ear canal.

Treatment of external otitis is like treatment of dermatitis elsewhere. *However compressing of the ear canal is not feasible* and routines which permit the patient to clean the canal are fraught with some peril. There are times when the ear canal needs to be cleaned of crusting and wax by the physician, but this should be kept to a minimum. If irritation of the canal by the physician and the patient can be eliminated, the exudation will usually soon cease. Topically the use of hydrocortisone has been of considerable help Where the factor of secondary infection seems important, the combination of topical antibiotics such as a combination of neomycin, bacitracin, and polymyxin, plus hydrocortisone, may be very effective. Sedation for a time to control the itching is worth considering Usually once the dermatitis has subsided, the crusts or other debris will find their way out of the canal. Occasionally the canal needs to be cleaned, and this should be reserved for the otologist. Systemic antibiotics are rarely needed in this condition.

Nonspecific Secondary Infection. Numerous skin conditions, particularly where there is any disruption of the intact surface or where the factor of pruritus exists, are subject to secondary infection. The wonder is that such infections are not more common. Ulcers such as varicose ulcers or traumatic ulcers due to burns, chemical injuries, or mechanical injuries not uncommonly

are the site of secondary infection. Often attention to the infection will bring about healing of these lesions which previously had remained open. Eruptions in which excessive perspiration with its attendant maceration as a factor are subject to secondary infection. Thus an intertriginous dermatitis of the axilla, groin, or submammary region may require antibacterial measures. Also, a dermatitis of the feet, whether a manifestation of a fungous infection or an eczema, may be associated with maceration and infection.

Pruritus, too leads to infection. In scabies and pediculosis, impetigo is a common accompaniment. In patients who have impetiginized areas on the trunk and extremities, a search for scabies is essential. Also, impetigo of the nape of the neck and scalp or pubic area should immediately arouse the suspicion of pediculi. Atopic dermatitis will at times also lead to secondary infection, and here too it is surprising that it is not more common.

In summary then, the practitioner who treats skin diseases must always be conscious of the cutaneous bacterial infections both as a primary or secondary condition. He should bring a critical mind to his evaluation of a skin condition and look for definite characteristic signs on which to base his conclusions.

Treatment of such lesions rests on the dual principle of elimination or control of bacterial invaders without irritation or sensitization of the skin and damaging of the natural defense of the host.

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where usually a manifestation of such entities as atopic dermatitis contact dermatitis, seborrheic dermatitis, and psoriasis. Pruritus plays a major role and is often the initial symptom. Scratching or irritating the external ear canal with such instruments as a cotton applicator hairpin, matchstick, or a well tapered fingernail is practically the rule in these patients. Often they have been conditioned from early life in the insertion of some object into the ear canal to clear it of wax and debris. This local irritation is often the starting of the dermatitis. Topical application of various home and drugstore remedies may further aggravate the itching and inflammation. Nervous tension may rapidly add its effect to the establishment of a continued pruritus. Sometimes the physician may continue the process by starting the patient on a routine of treatment of the ear canal.

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Edwin T Wright

21

SUPERFICIAL FUNGOUS INFECTIONS

Mycotic infections should be considered in about 30 per cent of the cases observed in the average dermatologic practice [1] and it has been stated that fungous infections are among the five commonest cutaneous diseases [2] Thus it is apparent that mycology should be of considerable interest to the dermatologist as well as to physicians in general.

The primary objective of this paper is to discuss therapy· however it is impossible to do this adequately without discussing to some extent causation, clinical description, and in some of the entities pathogenesis and epidemiology

In general, the discussion of therapy will be limited to accepted modalities with no attempt to present the many experimental drugs currently in the process of being evaluated. Suggested topical preparations are listed in the Appendix.

Cutaneous fungous infections may be classified in several ways, however in this presentation it is more practical to classify them from the clinical standpoint according to area of involvement than by the specific causative agent. This is because the same fungus may produce a variety of clinical pictures in different locations, and several species of fungi may produce a similar

clinical picture in one location. Hence the regional approach will be used in this presentation.

TINEA PEDIS ("athlete's foot"; dermatophytosis)

Infecting Agents. These are species of *Trichophyton* and *Microsporon*, *Epidermophyton floccosum* and *Candida albicans*.

Clinical Description. The extent and severity of the lesions depend on many factors. The two most important are the causative organism and the resistance of the host. *Epidermophyton floccosum* commonly produces areas of subacute erythematous scaly dermatitis, whereas lesions due to *C. albicans* are often exudative and macerated with fairly well-marginated borders ringed by small vesicles. *Trichophyton mentagrophytes* may produce an acute vesicular eruption between the toes and on the soles and sides of the feet. The lesions are moist, fissured, and macerated, predisposing to cellulitis due to bacterial invasion. *Trichophyton rubrum* usually produces a chronic infection characterized by hyperkeratotic thickening of the skin. Vesicles and inflammation are usually but not always absent. The advancing border may be slightly raised and red.

Epidemiology. There is a difference of opinion regarding the importance of exogenous sources of infection in the management of tinea pedis. Ajello and Getz [3] isolated *T. mentagrophytes*, *T. rubrum* and *E. floccosum* from used shoes and a shower stall. It was their opinion that effective control measures should include both the treatment of infected persons and the simultaneous eradication of the organisms in shoes and in the environment. Baer, in discussing this paper, stated that most of the evidence seemed to indicate that the important factor is the individual's susceptibility. This in turn is related to many factors such as moisture, sweat, type of footgear, and individual resistance.

Baer and coworkers [4–6] have shown that the foot skin of most persons has the capacity to rid itself rapidly of, kill, or inhibit pathogenic fungi similar to the self-sterilizing properties of the skin against bacteria. They point out that viable fungi are constantly and readily shed from clinically or subclinically infected feet. Therefore, frequent exposures and reexposures of

the feet to these fungi are practically unpreventable. The authors state that it is desirable to differentiate between asymptomatic fungous infection and fungous disease of the feet (dermatophytosis) The common dermatophytes are facultative pathogens that are frequently present on clinically healthy skin. These organisms cause disease only when favorable local conditions exist.

Strauss and Kligman [7] in an experimental study of tinea pedis and onychomycosis of the foot, found that the soles and nails are the stable reservoirs of organisms and are the chief sources of acute attacks. They state that primary infections are exogenous but reinfection is endogenous, that is, the patient himself is the source for reinfection or relapse. Many investigators are in agreement with this. From the above studies it seems apparent that control and prevention of fungous infections of the feet are best accomplished by attempting to maintain the local resistance of the individual rather than by attempting to sterilize shoes, showers, etc.

Therapy Chronic infections usually require little attention. In general the use of a powder during the day and an ointment at night will suffice Obviously the foot should be cleansed before applying either the powder or ointment.

Dry hyperkeratotic lesions due to *T rubrum* are more difficult to manage, especially when the infection involves the plantar surface of the foot. Topical fungicidal preparations are of little value exceptions are those which produce marked peeling, such as ointments containing salicylic acid. Since the fungi reside in the stratum corneum, anything which will remove this will also remove the fungus. However even continuous peeling fails to cure most cases. Recently Johnson and Tuura [8] found triacetin to be efficacious in infections due to *T rubrum* in 8 out of 12 cases.

Acute inflammation produced by the dermatophytes should be managed as are other acute inflammatory processes. This means putting the skin at rest and, if necessary putting the patient at complete bed rest, together with the appropriate local and systemic therapy Continuous compresses of potassium perman-

ganate 1:4,000; Burow's solution 1:40; or 0.25% silver nitrate solution will greatly reduce the inflammation and dry up moist areas. These should not be used to the point of producing excessive drying so that cracks and fissures develop. Mechanical debridement should be carried out as needed. When using intermittent compresses or soaks, a thin layer of an oil in water type of ointment will prevent excessive drying. In some cases hydrocortisone lotion or ointment may be used in place of standard therapy during the acute phase or combined with the more orthodox topical remedies. Sulzberger and Baer [9] report that there is no tendency for the infection to spread with the use of topical steroids; rather the suppression of edema, inflammation, and vesiculation discourages fungous spread. They have even used steroids systemically in rare instances in acute infections and have noted no tendency for the infection to spread. Occasionally secondary bacterial infection occurs resulting in a cellulitis and/or lymphangitis. This should be treated with the appropriate antibiotic, preferably not penicillin since dermatophytids have resulted from its use.

It is difficult, and in many cases impossible, to cure tinea pedis; however, acute exacerbations will become less severe and/or frequent if preventive measures are used. These include the use of powders and if necessary a mild fungicidal ointment or solution at night. Shoes should not fit too tightly and stockings of cotton or broad-mesh nylon are preferred. Broughton [10] studied tinea pedis in servicemen and found that *Trichophyton interdigitale* (*T. mentagrophytes*) could survive for at least 5 months in a laundered wool sock and then grow under moist conditions, the only medium being the sock fibers and desquamated scales. Skin cells in wool socks were stained with carbolfuchsin dye and traced through six consecutive launderings. Broughton states that fungi persist longer in wool socks and, in addition, wool absorbs sweat, providing a saturated moist atmosphere and an insulation to heat. He prefers broad mesh nylon, since it is nonabsorbent and is therefore porous to sweat.

It is probably impossible to escape repeated exposures to fungi; therefore even the finding of fungi in wool socks after

several washings is not too significant. The type of footgear used is important, however because of the local effect on the skin of the foot.

It is sometimes beneficial to use Banthine, Pro-banthine, or related anhidrotic drugs in patients with tinea pedis who have an associated hyperhidrosis [11] since there is general agreement that moisture and heat favor the growth of superficial fungous infections.

TINEA CAPITIS

Infecting Agents. These are species of *Microsporon* and *Trichophyton.*

Clinical Description. The early lesions may be small papules which are perforated by broken, lusterless hairs. The lesions en large peripherally forming oval or irregular patches, at times indurated. Inflammatory areas may form to which the term *kerion celsi* has been given. Varying degrees of alopecia occur during the infection.

Epidemiology and Pathogenesis. The disease primarily affects children before the age of puberty· however adults are occasionally infected, this being especially true with infections due to *Trichophyton tonsurans.* Infection is spread by direct contact with infected individuals, animals, or fomites. Spontaneous cure generally occurs after varying periods of time, but infection may persist even into adult life when the causative agent is *T ton surans*

The immunology and pathogenesis of tinea capitis due to *Microsporon canis* and *Microsporon audouini* have recently been studied by Kligman [12–14] In an earlier investigative study Rothman [15] found that adult sebum was more fungistatic than that from children. He concluded that this was an important factor in the resistance of adults to ringworm of the scalp Kligman was unable to confirm this. In addition he was able to produce experimental infections of the adult scalp He described four phases in the natural course of experimental tinea capitis (1) an incubation period lasting a few days, (2) a period of enlargement of the original lesions and the development of new

ones lasting about 3 to 4 months (3) a refractory period of variable time during which the infection was static; and (4) an involutional period which may or may not be preceded by inflammation. The concept was advanced that tinea capitis comprises two distinct types of infection: (1) scalp infection and (2) hair infection. Either of these may exist alone, but they are frequently combined.

The refractory period is of particular interest therapeutically since once this phase has been reached, the possibility of additional spread is negligible. Hence, if the disease has been present for less than 3 to 4 months, x ray epilation (if contemplated) should be withheld, since the refractory period has not been reached and *recurrence or reinfection may take place*

The futility of applying presently available topical fungicides is shown in part by his histopathological studies It is seen that the fungus invades and actively proliferates down to the upper limit of the keratogenous zone of the hair a level far below the penetrability of topically applied fungicides.

Therapy The treatment of tinea capitis leaves much to be desired, however, treatment is recommended, since it probably decreases contagion. In general the management of tinea capitis will vary somewhat depending on the age of the patient and the type of infecting fungus.

In children infected with *M canis* and *M audouini* the following is suggested The hair should be clipped short, and a skullcap made of washable material should be worn at all times. This may be difficult or impractical to do in the case of older female children. Topical fungicides should be applied twice daily These should not be too greasy and difficult to wash out. The ointment should be applied in a thin layer and rubbed in well. A list of suggested ointments will be found in the Appendix. Manual removal of infected hairs may be done two or three times weekly

If a kerion develops, it should be treated with wet dressings such as Burow s solution 1 40 or potassium permanganate 1 8,000. Strong fungicidal ointments should be avoided, since their use may precipitate local as well as generalized reactions, which are

manifested at times by an increased inflammation and swelling of the lesion and by a variety of generalized eruption most commonly morbilliform, fever and leukocytosis may also occur

Secondary infection, if present, should be treated with topical antibacterial ointments such as Neosporin. If necessary one of the broad-spectrum antibiotics may be used systemically Penicillin is not recommended, since its use may be followed by allergic reactions of various types.

Epilation by the use of x ray may be required for infections due to *M audouini*. This is usually necessary for infections due to *T tonsurans* but rarely for infections due to *M canis* Epilation should not be done until the refractory period has been reached as mentioned previously

Treatment must be considered for 3 months or longer The course of the disease may be followed by the use of the Woods light in those infections produced by fungi which fluoresce, e.g., *M canis* and *M audouini*. Before a cure can be presumed it is desirable to obtain three negative cultures taken at 27 week intervals

TINEA CRURIS

Infecting Agents. These are *E floccosum C albicans* and species of *Trichophyton*

Clinical Description. The upper and medial portions of the thighs are primarily involved, with occasional extension to the pubic area. The eruption is usually sharply marginated, the borders slightly elevated and more inflammatory than the rest of the lesion. Small vesicles may be seen at the margins, the whole area may be somewhat scaly and there is little tendency to central clearing. The affected areas have a brownish hue overlying the inflammatory process. The disease is most often bilateral, and pruritis may be quite annoying.

Therapy In acute cases 3% Vioform cream or 3% Vioform in a standard shake lotion will be beneficial. One per cent hydrocortisone added to the Vioform shake lotion or cream will give rapid symptomatic relief as well as decrease the inflammatory reaction. If the individual perspires freely or is quite obese,

lotions and/or powders are preferred during the day reserving the ointments for application at night. Pragmatar or 2 to 3% sulfur and salicylic acid in an emulsion base are quite satisfactory as ointments Those infections due to *C albicans* frequently respond best to Mycostatin powder in a shake lotion or to Castellani's paint. Verdefam and triacetin may be used for infections due to *T rubrum*.

TINEA CORPORIS

Infecting Agents. These are species of *Trichophyton* and *Microsporon*.

Clinical Description. The disease affects the nonhairy or glabrous skin. There may be one or several lesions which begin as small, roughly circular erythematous, scaly areas and enlarge slowly by peripheral extension with a tendency to central clearing. The advancing slightly elevated border may contain small vesicles or pustules. Some of the lesions may present an eczematoid picture and be diagnosed as eczema. *Trichophyton rubrum* may cause a granulomatous folliculitis, a condition most commonly observed on the lower extremities of women who shave their legs. In this condition the primary focus is frequently on the feet. Pruritis may be present especially in hot weather

Tinea corporis [16] is most frequently seen in three groups of individuals (1) persons who may be repeatedly exposed to infected domestic animals, e.g., kittens, cattle (2) persons with chronic fungal infections of the feet and nails; and (3) persons who are in close and regular contact with humans suffering from certain types of fungal infections.

Therapy Exfoliation or peeling of the stratum corneum is the main purpose of topical therapy This may be accomplished with the use of sulfur-salicylic ointments, diluted iodine solutions, Castellani's paint, or benzoic acid–salicylic acid ointment (Whitfield's ointment) When tinea corporis presents the clinical picture of an eczema, milder preparations should be used, such as one-fourth to one-half strength Whitfield's ointment or one of the fatty acid preparations such as Sopronol and Desenex. If the clinical picture is one of scaling, hyperkeratosis, and mild

erythema as is produced by *T rubrum* stronger topical preparations may be used such as full-strength Whitfield's ointment. Olansky and Callaway [11] have found Verdefam and triacetin the most satisfactory agents for retreatment of infectious *T rubrum*.

TINEA BARBAE

Infecting Agents. These are species of *Trichophyton* and *Microsporon*.

Clinical Description. Only adult males are affected. In some respects the infection resembles tinea capitis, since the beard hairs are similar to scalp hairs, having a long growing phase. Tinea barbae still occurs but is much less common than a number of years ago.

The lesions may present as erythematous annular rings, deep inflammatory follicular pustules which are essentially kerions, or follicular pustules which are clinically indistinguishable from chronic bacterial folliculitis.

Therapy Annular lesions will usually respond to sulfur-salicylic acid ointments. The inflammatory kerion type of lesion should be managed similarly to kerion of the scalp

The follicular pustular type of infection is often resistant to topical therapy and x-ray epilation may be required. This is not without some hazard, however and in some cases the persistent use of topical fungicidal ointments combined with manual epilation of the infected hairs will be the best and most advisable method of treatment.

TINEA MANUM

Infecting Agents. These are species of *Trichophyton* and *Microsporon, E. floccosum* and *C albicans*.

Clinical Description. Two main types of infections occur namely the inflammatory vesicular and the noninflammatory squamous types. The latter is most often due to *T rubrum*.

Therapy The vesicular *inflammatory type is managed similarly* to any eczematous process, with the use of soaks or compresses. After the inflammation has subsided mild fungicidal ointments

may be used. The noninflammatory scaly hyperkeratotic type of infection due to *T rubrum* is usually quite resistant to treat ment. Verdefam, triacetin, or half to full-strength Whitfield's ointment may be of some benefit.

ONYCHOMYCOSIS

Infecting Agents. These are species of *Trichophyton*, *E. floccosum*, and *C albicans.*

Clinical Description. The disease is not uncommon and is frequently associated with some form of tinea pedis or tinea manum. When due to *C albicans* there is frequently some evidence of candidiasis elsewhere.

The nails become dry brittle, lusterless, ridged, pitted, and discolored. Detritus consisting of fungous elements and desquamated cells may accumulate beneath the nails in those infected with species of *Trichophyton* and *E. floccosum*. Infections caused by *C albicans* produce very little detritus, and commonly a nonpurulent paronychia is present.

Pathogenesis. Lewis [17] in an excellent study of the fetal and mature nail, divides the nail into three layers the superficial layer or dorsal nail, the main nail body or intermediate nail, and the deepest layer or ventral nail. Jillson and Piper [18] in a histologic study of human infected nails, found that pathogenic and saprophytic fungi were located in one or more of these specific layers. They found *T mentagrophytes* to be located in the surface or dorsal, layer and *T rubrum* to be in the deepest or ventral layer and occasionally in the intermediate layer Saprophytic fungi were located in the surface, or dorsal, layer Sagher [19] in an earlier study also found *T rubrum* in the deepest, or ventral, layer of the nail. He observed that *T rubrum* never entered the nail from the superficial layer as did *Trichophyton violaceum*. *Trichophyton rubrum* proliferated in the opposite direction to that of the nail growth, however when the fungus entered from the region of the lunula, it grew in the same direction as the nail. A knowledge of some of these basic studies helps us understand why therapy of onychomycosis, especially that due to *T rubrum*, is so unsatisfactory

Therapy Fungous infections of the nails produced by *E floccosum* may be treated with any of the standard fungicidal ointments available for use in tinea pedis. This is also true for infections caused by *C albicans*, however in addition to these the use of nystatin in ointment form may be of considerable value. There may be an associated paronychial infection which necessitates the minimal use of soap and water In general, the nails should be kept as dry as possible, since moisture favors the growth of *C albicans*.

Infections due to *T rubrum* are extremely resistant to treatment. Unfortunately most cases of onychomycosis are due to *T rubrum* and frequently there is an associated infection of the feet and/or hands. The latter provides a constant endogenous source for reinfection of the nails. Topical therapy is of little value in most cases however triacetin and Verdefam may be used with some benefit in an occasional case Recently Onycho-Phytex has been used by a number of investigators. This may be of some value; however it is too early to say whether the initial benefits observed will be maintained. At times it is desirable to remove the infected nail, however it is quite common for the new nail to become infected in time. In many cases all that can be done is to decrease the cosmetic effect of deformed nails by constant filing of the infected nails two or three times weekly in conjunction with the use of one of the previously mentioned topical fungicides.

TINEA VERSICOLOR

Infecting Agent. This is *Malassezia furfur*

Clinical Description. This is a chronic, usually asymptomatic or slightly pruritic infection of the glabrous skin. The lesions begin as small, slightly brown patches and involve primarily the chest, back, and neck but may at times involve the extremities. There is little or no inflammation, and scaling is very superficial. The lesions fluoresce a yellow brown when viewed under the Wood's light.

Therapy *Any topical preparation which produces peeling without producing disagreeable side effects is usually satisfactory*

These include the application of 20% sodium thiosulfate solution once or twice daily 3% salicylic acid in emulsion base, Pragmatar and Fostex.

Treatment should be continued for 2 to 3 weeks after apparent cure, since recurrence is frequent.

ERYTHRASMA

Infecting Agent. This is *Nocardia minutissima.*

Clinical Description. The disease commonly involves the axillary and inguinal areas. The lesions vary in size from small to large well-circumscribed brown-red scaly patches. The scales are fine and branlike. The underlying skin may be quite erythematous, and a serpiginous outline is produced as the lesions spread peripherally The affected areas are usually asymptomatic; however in individuals with hyperhidrosis pruritis may occur

Therapy Treatment is similar to that of tinea versicolor with the exception that greasy ointments should be avoided. Ointments containing a water washable base are preferred, e.g., Pragmatar

TRICHOMYCOSIS AXILLARIS (LEPOTHRIX)

Infecting Agent. This is *Corynebacterium tenuis*

Clinical Description. In this disease the causative bacillus forms dense colonies on the surface of axillary and pubic hairs. The hair shaft is not invaded by the organism, nor does the hair break off as occurs in fungous infections of the hair Clinically these colonies of bacteria on the hair shaft appear as yellow concretions or nodules.

Therapy The affected areas should be shaved and an antibiotic ointment applied. In the past fungicidal ointments were used, since it was thought that the causative agent was a fungus. Daily washing with soaps or detergents containing hexachlorophene will aid in preventing a recurrence.

CANDIDIASIS (MONILIASIS)

Infecting Agent. This is *Candida albicans.*

Clinical Description. Candidiasis is primarily a mucous mem-

brane or cutaneous disease. Systemic involvement occurs, however a discussion of this is not within the scope of this paper

Clinical candidiasis may appear in several different forms. On the skin it usually begins in the intertriginous areas where there are two apposing skin surfaces such as in the axilla, genital region, groin, interdigital spaces, under the breasts, and at the angles of the mouth—in short, areas of the body which may be moist and in which, through maceration and friction, a breakdown of skin occurs. Involvement of the mucous membranes appears most commonly as thrush of the mouth and vaginal or vulvovaginal candidiasis

Thrush is seen primarily in infants, debilitated children, and in adults suffering from acute or chronic diseases, e.g., diabetes, pemphigus, malignancy Candidal vaginitis and/or vulvovaginitis is most frequently seen in women with chronic cervical infections, cervical lacerations, and in association with coexisting diabetes, malignancy etc. Pregnancy is a well known predisposing cause. Lang and Stella [20] state that about 30% of their obstetric outpatients have positive cultures for *C albicans* and about 5% have symptomatic candidal vulvovaginitis. Pace and Schantz [21] in a study of 76 unselected office patients whose complaint was pruritis and leukorrhea, found *C albicans* to be the causative organism in 59 subjects. Thirty-one were pregnant and twenty eight were nonpregnant.

Thrush and/or candidal vulvovaginitis may follow the prolonged use of ACTH, the corticosteroids (cortisone, prednisone, etc.) and the broad spectrum antibiotics, both topically and parenterally

Not mentioned are candidal paronychia and *pruritis ani*. The former is seen in housewives, bartenders, dishwashers, and in others in occupations in which the hands are immersed in water frequently resulting in a moist skin which favors the growth of candida. Pruritis ani may result from candidal infection of the anal area. Though not a major cause, some cases of "incurable pruritis ani are cured by treating the candidal infection.

Epidemiology and Pathogenesis. *Pillsbury et al. [18] state*

that *C. albicans* exists most commonly as a harmless colonist on abnormal skin or on normal or abnormal mucous membranes. Thus clinical candidiasis will be seen only when there is a lowering of the host's resistance, either local or general. Local factors include maceration, friction, moisture, and dermatitis from other causes, i.e., any condition which breaks down the normal integrity of the skin or mucous membranes. Systemic diseases, e.g., diabetes, acute and chronic infections, or malignancy may lower the general resistance and allow *C. albicans* to proliferate.

It is generally accepted that *C. albicans* may be found in the normal mouth, normal vagina, and in the stool of normal individuals. Blank [22] states that *C. albicans* may be recovered from the crevices of the body including the gingiva and the vagina, and from the feces in more than half the population. This being true, it is apparent that the most important factor in the development of candidal infection is the host's resistance, as previously mentioned, since the organism is often ever-present.

Therapy. Ordinarily cutaneous candidiasis is most frequently seen in the intertriginous areas; hence, greasy preparations are contraindicated. Powders, lotions, paints, and nongreasy ointments are used. Some of the more useful preparations are 3% Vioform cream or Vioform powder 3% in a standard shake lotion. Nystatin may be used in ointment form (Mycostatin ointment) or in a shake lotion. The inflammatory reaction and associated pruritis may be greatly relieved by using topical hydrocortisone in addition to the usual antifungal medications, e.g., Vioform-hydrocortisone cream. Castellani's paint, either half or full-strength, is especially valuable in candidal infection of the groin. The skin should be kept as dry as possible, since the growth of *C. albicans* is aided by a moist environment.

Candidal paronychia may be quite resistant to treatment, especially in individuals whose occupations require them to get their hands wet frequently. Treatment should be directed toward keeping the hands dry together with the application of topical fungicides. Mycostatin ointment has been the most beneficial in our experience. A primary focus of candidal infection should

be looked for such as mouth or vagina, and, if present, treated, since reinfection from these sources is not uncommon.

Candidal granulomas of the skin are fortunately uncommon, since their treatment is difficult. The use of nystatin in tablet form in large doses orally as well as in ointment form locally is recommended. Careful debridement should be carried out, since the efficacy of nystatin depends largely on getting it in contact with the yeast itself

Thrush has been treated with many different preparations, the best example being 1 to 2% aqueous gentian violet. The main disadvantage of this preparation is the staining which accompanies its use. Nystatin powder dissolved in water (Mycostatin for suspension) may be used as a mouthwash, or the tablets may be used, allowing one tablet to dissolve slowly in the mouth three to four times daily

Candidal vaginitis and vulvovaginitis may be treated with gentian violet suppositories (Genita Jel) or nystatin suppositories. In resistant cases it may be necessary to administer in addition nystatin orally in a dosage of one tablet (500,000 units) three to four times daily for 2 to 4 weeks. Topically Vioform hydrocortisone cream may be applied to the vulva and perineal area. Relapses occur and are most frequently seen in patients with some predisposing cause, e g., diabetes, chronic cervicitis, malignancy Reinfection may occur from fomites such as douche tips. Husbands may become infected from their wives and in turn reinfect their wives after the latter have been treated. Obviously in these situations the husband should be treated.

APPENDIX

The following is a list of suggested topical preparations

Powders

Desenex
Sopronol
Vioform

Lotions and Liquids

Mycostatin lotion
Vioform lotion
Verdefam
Onycho-Phytex

Ointments

Desenex
Sopronol
Pragmatar
Enzactin (triacetin)
Vioform cream and ointment
Vioform-hydrocortisone cream
Asterol
Quinolor compound ointment
Salundek
Whitfield's ointment (N.F. IX)

salicylic acid	60/0
benzoic acid	120/0
wool fat	50/0
white petrolatum	q.s.1,000/0

Mycostatin ointment

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Victor D. Newcomer
and Carlyn Halde

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SYSTEMIC MYCOSES

The systemic mycoses have had until recently a dismal and hopeless prognosis. Recently acquired knowledge concerning the epidemiology of these infections, their total disease spectrum in man, the increased interest in developing antifungal drugs, and the availability of several such drugs has, in many instances, caused a more optimistic outlook toward the management of these diseases.

Studies utilizing new techniques for the isolation of pathogenic fungi from soil have provided ample evidence that many of these fungi exist as saprophytes over large but still delineated geographic areas of the world [1]. Such studies have further demonstrated that the habitats of these organisms are not evenly distributed throughout these areas but are rather sharply localized to specific sites, with surrounding areas being relatively free of organisms. For example, *Histoplasma capsulatum* has been repeatedly isolated from many soils including certain chicken yards and abandoned silos, notably in the Middle Western and Eastern United States [2–4]. *Coccidioides immitis* has been found in soils in the arid and semiarid regions of the Southwest, oftentimes in the vicinity of rodent burrows [5]. There is pre-

liminary evidence which suggests that the growth of these organisms in such areas may be influenced by many factors. For example, in the endemic areas of the Southwest, dust control programs and agricultural practices, including type of crop cultivation, irrigation practices, and the application of commercial fungicides to crops and soil, may influence the incidence of coccidioidomycosis in man [6]

Early descriptions of the systemic mycoses were of the more obvious and serious forms Recent detailed skin-testing programs involving large segments of human, and in some instances, animal residents of specific areas have not only further delineated geographic areas of endemicity but also have indicated that in such areas large segments of the human population acquire sensitivity either as the result of an asymptomatic exposure or of an infection that was of such mild or short duration as to pass undiagnosed. In coccidioidomycosis and histoplasmosis this is particularly true [7–9] Thus, in these two diseases, the disseminated and progressive forms are now known to represent only a small fraction of the total disease spectrum, and even within this group the recent acquisition of more clinical experience has demonstrated that cases which were formerly considered as hopeless will respond, and in some instances dramatically to prolonged and optimal symptomatic therapy

The growing list of medicaments which have favorably influenced the course of serious systemic bacterial disease has produced a tremendous stimulus to the search for specific antifungal antibiotics and other antifungal compounds. Extensive in vitro testing programs indicate that there are many compounds which possess fungicidal properties. Relatively few however favorably influence the course of experimentally induced fungous infections in animals, and even fewer possess characteristics which permit administration to humans.

The evaluation of such antifungal agents at a clinical level is extremely difficult for many reasons among which are (1) lack of a thorough understanding of the natural course of the disease (2) scarcity of large numbers of patients and (3) the difficulties involved with prolonged periods of observation. When dealing

with human material, such serious limitations understandably may occasionally lead to early conflicting views and opinions with regard to the value of given therapeutic modalities. Nevertheless, there are at present several antifungal agents which have demonstrated promise in certain of the mycoses and are now in the stage of more extensive and definitive clinical evaluation.

ACTINOMYCOSIS

Actinomycosis is a disease with protean manifestations, the most frequently recognized type being a chronic granulomatous variety with characteristic hard woody lesions which subsequently break down and form multiple sinus tracts. Actinomycosis is said to be one of the more common of the systemic mycoses and is world-wide in distribution. Once the disease is suspected, the diagnosis may be confirmed by finding colonies of the fungus in the form of sulfur granules in the abscesses or draining sinuses or in histological sections of biopsy material [10]

This disease is caused by *Actinomyces bovis*, an organism unique among the pathogenic fungi in that it must be cultured anaerobically Actinomycosis is thought to be acquired endogenously as the organism has frequently been cultured from carious teeth, crypts of tonsils, and other areas in the mouth.

Inorganic iodine in the form of potassium iodide or sodium iodide has been recommended for many years as the treatment of choice for actinomycosis, but current opinion indicates that it is of little or no value, and former cures merely related in most instances to the normal excellent prognosis of some types of the disease Cope, for example, in reviewing the world's medical literature on actinomycosis in 1938, before the sulfonamide and antibiotic eras, estimated that 97 per cent of the infections in the cervicofacial area recovered [11]

Today therapy utilizes antibiotics along with adequate surgical management where this is indicated. Penicillin has received the most extensive usage and remains the drug of choice. High dosages in the order of 1,000,000 to 5,000,000 units per day are recommended and should be continued for at least a month after

a clinical cure has been achieved [12]. We have, however, in selected cases, used dosages as high as 15,000,000 units daily. If no effect is noted within a period of 2 weeks, attempts should be made to reevaluate the predisposing factors as well as to re-isolate the organism and to determine its sensitivity to other antibiotics and sulfadiazine. The tetracyclines, streptomycin, and erythromycin have been reported as being effective against actinomycosis and may be of definite value as a substitute in the treatment of actinomycosis when the patient has or develops a sensitivity to penicillin or may be employed concomitantly with penicillin therapy where associated bacteria are penicillin-resistant. Several cures with isoniazid [13, 14] and one with stilbamidine [15] have been reported.

NORTH AMERICAN BLASTOMYCOSIS

North American blastomycosis is a granulomatous disease caused by *Blastomyces dermatitidis* [10, 16]. The disease is predominantly one which is acquired in the Central and Eastern portions of the United States; however, ease and rapidity of travel demands its diagnostic consideration in all areas. As in the case of all the systemic mycoses, dissemination by contagion has not been demonstrated, and this organism has, therefore, been suspected of being a soil or plant saprophyte in nature. It has not been isolated to date, however, from such sources. An absolute diagnosis demands the demonstration of refractile, thick walled cells, 5 to 20 μ in diameter, alone or with a single bud, in clinical material and subsequent cultural confirmation. Skin and serological tests alone are of limited diagnostic value.

The disease has been traditionally divided into the systemic and cutaneous types. The systemic form is characterized by an initial pulmonary infection with subsequent progressive dissemination to practically all organs with a predilection for the skin and bones. The cutaneous type was formerly considered to be the result of a direct inoculation into the skin, but current opinion supports the concept that the majority of such cases have resulted from dissemination from a pulmonary focus [17, 18]. Skin and complement fixation tests are of aid in ascertaining the

status of the infection and the prognosis. Serum, for example, which is high in complement-fixing antibodies and which is associated with a negative reaction to skin test suggests a poor prognosis, whereas serum with a low complement fixing titer or the lack of such antibodies associated with a positive reaction to skin test generally indicates a more favorable prognosis [16, 19]

Traditionally potassium iodide was employed together with vaccine therapy for the treatment of blastomycosis. This mode of therapy left a great deal to be desired in respect to its ultimate curative value and in some instances was detrimental in that the treatment was associated with an exacerbation of the disease. Roentgen therapy hastens the involution of cutaneous lesions but should never be employed alone, as it has no curative value. Surgery has in the past been credited with cures in cases of small localized lesions amenable to this type of approach. All the currently available antibacterial antibiotics have been used for the treatment of blastomycosis, but none have proved efficacious, although they are of value for the control of secondary infection.

Several antifungal drugs are currently being evaluated for their efficacy against blastomycosis. Some of the aromatic diamidines have been found to modify the course of blastomycosis effectively Propamidine was originally used for the treatment of blastomycosis [20] but experience indicated that it was too toxic for systemic use. Stilbamidine then received extensive trial, but its administration was frequently followed by the development of a late chronic and unique neuropathy generally confined to the face [21] 2 Hydroxystilbamidine subsequently completely replaced stilbamidine in the treatment of blastomycosis, as the administration of this drug was not associated with the development of these neuropathies [22] It is administered intravenously in a daily dose of at least 225 mg dissolved in 500 ml of 5% glucose over a period of 30 to 50 days. The drug has been given in dosages as high as 450 mg per day without any untoward reactions [16] Early reports of a high cure rate, however have been tempered with a higher relapse rate than has been generally recognized. As a matter of fact, Harrell and Curtis speculate that

perhaps it is the natural immunologic response to the disease process more than anything else that governs the favorable or unfavorable response to present day stilbamidine treatment [22]

Several antifungal antibiotics have become clinically available in sufficient amounts to be used for the treatment of blastomycosis. Nystatin has not been demonstrated to be of value in the treatment of this disease, but amphotericin B an antifungal antibiotic recently isolated from an unidentified species of *Streptomyces* has been reported to influence favorably the course of blastomycosis.

Harrell and Curtis have recently reported their experience in the treatment of four male patients with severe systemic stilbamidine-resistant North American blastomycosis with Amphotericin B They observed complete healing of the cutaneous lesions in 3 weeks of antibiotic therapy There was also complete disappearance of the causative organism, *Blastomyces dermatitidis* from the sputum and/or skin in all four cases [23]

Surgical procedures are recommended for the purpose of draining large pockets of pus. Cutaneous laryngeal, prostatic, and urinary lesions have been excised to reduce the possibility of further dissemination. Resection of the lung has been undertaken for localized pulmonary lesions without dissemination and for lesions which have persisted after diamidine therapy

NOCARDIOSIS

Nocardiosis is a granulomatous disease which has been confused with tuberculosis and actinomycosis in the past. The disease is world wide in distribution and is caused by several species of *Nocardia* [10] *Nocardia asteroides* and *Nocardia brasiliensis* are the two most common organisms causing the disease in North America They have been frequently cultured from soils, and infection is thought to be acquired by inhalation of dust containing the organism or by direct inoculation of contaminated material into the skin.

Pulmonary infections may closely simulate tuberculosis or actinomycosis. Neurological manifestations may be, however the presenting symptom in some instances as the result of a predilec-

tion for early dissemination to the central nervous system [14] The incidence of nocardiosis appears to be increasing in individuals as a terminal event during the cachectic period of fatal diseases.

Localized forms of the disease have been described in the past as mycetoma, or "madura foot. These are characterized by the development of localized, hard, indurated areas, usually of the extremities. These may slowly progress and produce extensive deformities. The area usually contains multiple nodules and draining sinuses, and underlying bony structures are generally involved in the disease process.

The diagnosis of nocardiosis is dependent upon the identification of the organism. It is readily cultured, and the colonies are quite distinctive. Although the organism forms sulfur granules in tissue, individual filamentous bacillary or diphtheroid forms may also occur and because of their partial acid-fastness have been confused with *Mycobacterium tuberculosis* Early diagnosis has been stressed, because the early and localized forms of the disease are more amenable to therapy

Those infections caused by *N asteroides* have been most successfully treated with the sulfonamides, especially sulfadiazine and sulfamerazine [12] Sulfadiazine, alone or in combination with sulfamerazine, is given to produce blood levels of 10 to 20 mg per 100 ml (4 to 6 gm per day) as long as clinical evidence of the disease is present. A severely ill patient may require an even higher dosage A lower dosage is continued for 3 to 4 months after apparent clinical cure to prevent a relapse. Adequate surgical drainage and excision are valuable adjuvants where indicated. Peabody and Seabury suggest combined sulfonamide and antibiotic therapy since most strains of *N asteroides* are sensitive to antibiotics [12] They believe that 2 gm of streptomycin should be added to the regimen until appropriate sensitivity tests indicate that therapy should be modified. Sensitivity tests may be deceptive, since in vitro certain antibiotics may lack a suppressive effect which is evident in vivo [25, 26]

Infections due to *N brasiliensis* are encountered with great frequency in Mexico. DDS (4,4'-diaminodiphenolsulfone) is the

most effective agent presently available for the treatment of infections due to this organism. One hundred milligrams are given twice a day until clinical evidence of the disease has disappeared, which usually occurs within a year but it is recommended that therapy be continued for a period of 2 to 3 additional years. Premature cessation of treatment is usually followed by a relapse and some of these patients have not improved with a second course of DDS therapy [27]

Sulfonamide and DDS therapy have not been effective in patients with central nervous system lesions, and those with thoracopulmonary involvement have a poor prognosis, although a few cures have been obtained. Prolonged therapy is necessary to treat mycetoma, and amputation has become less frequently necessary

CRYPTOCOCCOSIS

Cryptococcosis, a disease world wide in distribution, has been described as one inevitably involving the central nervous system and eventually leading to death however exceptions are being encountered with greater frequency

The disease is caused by *Cryptococcus neoformans*, an encapsulated budding fungus, which has a marked predilection for involving the central nervous system. In recent years the organism has been found widespread in nature, leading a saprophytic existence Although once considered to be an aggressive invader it is now recognized that *C neoformans* is an opportunist frequently taking advantage of defective defense mechanisms in the host The disease has been associated with Hodgkin's disease and other lymphomas, and it has been found to coexist with such infectious diseases as tuberculosis, histoplasmosis, and coccidioidomycosis [28–31]

It is the current opinion that most cases of central nervous system involvement represent a dissemination from either a clinical or subclinical pulmonary lesion. The frequency with which metastasis occurs from pulmonary foci is purely speculative, as the incidence of pulmonary involvement is unknown. It is becoming increasingly evident, however that transitory infec-

tions limited to the lungs occur more often than was formerly suspected [32, 33]

Early suspicion and identification of obscure pulmonary infections is to be stressed as an important step toward treatment. The pulmonary form of the disease appears to be more amenable to therapy however once the organism has invaded the central nervous system, the prognosis is invariably fatal, with 80 to 90 per cent of such cases succumbing within 1 year Although there are presently several antifungal agents under therapeutic investigation which appear to be effective in vitro and in vivo in animals against *C neoformans* all have proved uniformly disappointing in human cases in which there has been involvement of the central nervous system. Reported cures with certain drugs followed by reports of failures with the same drug have led to the belief that perhaps spontaneous remissions were observed rather than cures. The effect of these agents in pulmonary cryptococcosis of man has not been evaluated and may offer considerable promise in such early diagnosed cases Amphotericin B which is currently under study has shown promise in one case [34]

The fear of dissemination has led to the recommendation of surgical extirpation as soon as possible after the diagnosis is firmly established [35, 36] It has been particularly recommended in instances of localized torulomas of the lung. Statistical data are not available to justify this radical approach in all cases. Pneumonitis in several patients has completely disappeared with supportive therapy together with the discontinuance of all antibacterial and antiinflammatory drugs.

SOUTH AMERICAN BLASTOMYCOSIS

South American blastomycosis is a progressive granulomatous disease of the mucous membranes, lungs, lymph nodes, skin, and viscera endemic in many parts of South and Central America.

The various clinical symptom complexes which occur are said to be dependent on the portal of entry One of the most common clinical types combines lesions of the oral mucosa, cervical lymph nodes, and lungs [37] Specific serologic tests have not

yet been standardized for diagnostic purposes, and diagnosis is dependent upon finding the characteristic multiple budding organism in tissue and its isolation by culture.

The disease was usually fatal prior to the introduction of the sulfonamides, but clinical remissions are now attainable, and a few cures have been reported [37] Large doses of the sulfonamides are frequently necessary to produce a remission, and in general the drug must be continued indefinitely if improvement is to be maintained. Sulfadiazine or sulfamerazine have been most successful. An initial dosage schedule of 1 gm every 6 hours is recommended, and the dosage is subsequently adjusted so that a blood level of 8 to 12 mg per 100 ml is maintained. This dosage is continued for weeks or months after the disappearance of all clinical manifestations, and then a maintenance dose of 2 to 3 gm daily is given indefinitely The inherent toxicities associated with these drugs present serious limitations to prolonged therapy In addition, good nutritional management together with the correction of any oral pathology has been strongly recommended [38, 39]

The newer antifungal agents such as amphotericin B may offer some promise in the treatment of this disease.

SPOROTRICHOSIS

The type of sporotrichosis most frequently encountered in the United States is a localized form characterized by the development of multiple subcutaneous nodules along the course of the lymphatics draining a chancre-like primary lesion. Less frequently seen are the disseminated forms of the disease. The causative agent, *Sporotrichum schenkii*, is generally thought to be introduced into the skin by trauma. It has been isolated from soil, wood and plants. Sporotrichosis has appeared throughout the world frequently in farmers, laborers, and horticulturalists [10]

The diagnosis is based upon the clinical appearance of the lesion and the isolation of the fungus in culture. The spherical to elongate budding organisms found in tissue are difficult to demonstrate.

Iodides are the drugs of choice for the treatment of sporo-

trichosis. The localized lymphangitic form of this disease responds favorably in most instances to early and intensive therapy. However, in those rare cases in which sporotrichosis has disseminated to various internal organs, the disease may not respond as favorably and in some instances progresses in spite of iodide therapy [40, 41].

Iodine is generally administered in the form of a saturated solution of potassium iodide. The initial dose is usually 10 drops three times a day in a glass of water or milk. This dose is rapidly increased by daily increments of 5 drops to each of the dosages throughout the day until the patient is receiving as much as 30 to 40 drops three times a day or until the limit of tolerance is reached. The average period of medication varies from 1 to 3 months, but medication should be continued for 1 month after the disease has subsided to prevent recurrence [42]. Surgical intervention in sporotrichosis is usually contraindicated, since increased suppuration and ulceration frequently follow. Stilbamidine and 2-hydroxystilbamide have been used successfully in the treatment of a few patients with sporotrichosis, but its exact status is still under evaluation [40–43].

HISTOPLASMOSIS

Histoplasmosis is an infection with a wide variety of clinical disease patterns [10, 44]. Early experience with the disease demonstrated that the causative organism was in tissue a small, budding fungus, *H. capsulatum*. Parasitism of the reticuloendothelial system characterizes the disease, the more severe forms of which are manifested by anemia, weight loss, irregular fever and hepatosplenomegaly. The disease was formerly considered rare and thought to be uniformly progressive and usually fatal.

From recent evidence acquired from large epidemiologic studies including chest x-ray surveys, skin testing, and cultural studies, histoplasmosis now appears to be one of the most common and widely distributed of the systemic mycoses [45]. Soil survey programs have isolated *H. capsulatum* from many sites in the Eastern and Central portions of the United States and from other parts of the world [1]. In such areas in the United States,

epidemiologic studies support the concept that most infections produced by *H capsulatum* are asymptomatic or of such a mild degree as to necessitate no medical attention. In some endemic areas, over 80 per cent of the children of high school age were found to possess a positive reaction to skin test for histoplasmin [8, 9]

The serious disseminated systemic form of this infection is seen most frequently in infants and in the age groups beyond forty Patients with lymphomas, particularly Hodgkin's disease, and those with other wasting diseases such as tuberculosis, appear to be susceptible to histoplasmosis.

From a diagnostic standpoint the most desirable evidence is the isolation of the organism from pathological materials by culture or by animal inoculation. This is, however at times difficult, particularly when minimal infiltrating areas of pneumonitis are the only physical finding. In such instances development of histoplasmin sensitivity and the observation of changing serological titers offer considerable diagnostic support.

The prognosis in the vast majority of instances is excellent in that the disease remains subclinical or runs a mild self-limited course In the progressive disseminated variety the prognosis for recovery is grave although spectacular remissions have been reported. To date no antifungal agent is available which consistently favorably influences the course of disseminated histoplasmosis.

Ethyl vanillate has been reported as showing promise in the treatment of histoplasmosis in children however its exact status as a therapeutic agent is still undetermined Lehan et al. have treated approximately 50 cases of histoplasmosis with various chemicals and antibiotics [46] No therapeutic effect could be demonstrated with the use of stilbamidines, disulfiram, nystatin, or 8-diethylaminoethyl fencolate Plotnick and Cerri [47] treated a case of oral histoplasmosis by the local intralesional injection of nystatin with complete disappearance of the lesion Preliminary clinical studies regarding the use of amphotericin B and amebacide indicate that they may be of some value for the treatment of disseminated histoplasmosis [45]

Recently Lehan et al. [53] reported four cases of disseminated and five cases of chronic progressive pulmonary histoplasmosis treated with amphotericin B. Good results were obtained in two of the disseminated cases receiving 40 to 55 infusions respectively of 50 to 100 mg of amphotericin B daily. The other two disseminated cases were moribund at the start of treatment and succumbed after only two or three infusions. The five chronic progressive pulmonary cases showed fair to good clinical response in all cases with moderate to marked x-ray improvement. It is their feeling that amphotericin B warrants further trial in the treatment of histoplasmosis both the acute and chronic progressive forms.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis in the United States is endemic in the arid and semiarid areas of the Southwest. The San Joaquin Valley in California and areas near Phoenix and Tucson in Arizona are perhaps the most well-known sites of endemicity. In certain sections of these geographic areas the rate of infectivity with the fungus may be as high as 10 per cent per year among the unexposed population as evidenced by conversion of skin tests with coccidioidin [7].

Coccidioides immitis, the causative agent, has been repeatedly demonstrated in soils of such areas. Infection is acquired, usually by inhalation of arthrospores. Since individuals traveling through the endemic areas have been known to acquire this disease, consideration as a diagnostic possibility is becoming increasingly important throughout the United States.

The disease spectrum varies from a mild nonspecific pneumonitis to a progressive chronic, disseminated granulomatous disease. Epidemiologic studies indicate that in approximately 60 per cent of the patients the disease has been asymptomatic or of a mild nature. Forty per cent of the infections were symptomatic to the extent that the patients sought medical aid. Of these only a small percentage developed the progressive disseminated type of infection. Smith et al. on the basis of studies on Army personnel estimates that dissemination takes place in

approximately 1 in 400 coccidioidal infections, or 1 in 100 cases of diagnosed disease in white adult males. The rate of dissemination among Negroes is at least ten times that of whites, and that of Filipinos is still higher [48]

The diagnosis is most firmly established by identification of the typical spherules of *C immitis* containing endospores in pathological material, with subsequent isolation by culture or in experimental animals. Although cross reactions occur the use and proper evaluation of skin tests, precipitin, and complement fixation tests are of considerable value in the diagnosis and prognosis of the disease. The combination of precipitin and complement fixation tests detected over 90 per cent of clinically manifest uncomplicated primary infections, but less than 10 per cent of asymptomatic infections, which were determined by skin tests. The serological tests confirmed three-fifths of coccidioidal pulmonary cavities and 99 per cent of disseminating infections. In those patients where dissemination takes place, the skin and complement fixation tests are of some aid in establishing a prognosis. Those possessing a positive reaction to skin test and a low complement fixation titer are thought to have a better prognosis for recovery than those with a negative reaction to skin test and a high persisting complement fixation titer [49, 50].

Supportive therapy constitutes the bulwark of treatment and current studies have reemphasized its effectiveness in modifying the course of disseminated coccidioidomycosis. Such therapy encompasses extended bed rest, good nutritional diet, and the correction of any other abnormality which has been elicited. Such therapy should be continued until evidence of active disease has subsided, including return of the temperature and sedimentation rate to normal, disappearance of humeral antibodies, and healing of any cutaneous or pulmonary lesions. Under such a regimen the acute primary pulmonary infections invariably heal and no further therapy is indicated.

The surgical resection of pulmonary residuals has become an accepted procedure and is indicated in circumstances such as severe hemoptysis, large or expanding cavities, cavities located in the pulmonary parenchyma where rupture into the pleural

cavity is a distinct possibility chronically secondarily infected cavities, and solid coin lesions of questionable diagnosis in patients demonstrating only a positive reaction to skin test [51]

A large number of antifungal drugs have been reported as favorably influencing the course of coccidioidomycosis in experimental animals and in man. Among these are prodigiosin, stilbamidine, 2 hydroxystilbamidine, diethylstilbestrol, methyltestosterone, combined androgen and estrogen therapy isonicotinic acid hydrazide, ethyl vanillate, Promizole, nystatin, and most recently amphotericin B [52] Because of the small number of cases, short periods of observation, and the normal course of this disease, which is characterized by chronicity with exacerbations and remissions, the value of many of these drugs for the treatment of coccidioidomycosis awaits further detailed study

Winn has recently stated that immunotransfusions or serum globulin preparations from recovered coccidioidal patients may be helpful [51]

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G Douglas Baldridge

23

COMMON VIRAL DISEASES OF THE SKIN

This chapter will deal primarily with the treatment of viral diseases of the skin. However in order to grasp fully the sense or nonsense of any proposed method of therapy one must have some basic knowledge of the nature of viruses. With this in mind, those background aspects of virology which will serve as a basis for the choice of proper treatment will be first discussed.

NATURE OF VIRUSES

Viruses are heterogeneous groups of organisms which attack not only animals but bacteria and plants as well. They require living cells for propagation and are completely dependent upon the host for all needs. This is shown by the fact that a tissue-free suspension of virus particles shows no evidence of "life" such as respiration. Because of this unique feature I call them "super" parasites. This intimate relationship between the organism and the host cells presents a severe stumbling block to the therapist as will be seen later on.

The structure of viruses varies widely within the group. The plant viruses seem to be composed of a single molecule of ribonucleoprotein and under certain circumstances can be actually

made to form crystals and be stored as such. Moving up the scale of size and complexity we find that "large" viruses, for example that of vaccinia, contain copper, carbohydrate, and other compounds in addition to the basic nucleoprotein. Members of the latter group (which includes most of the skin viruses) do not contain enzyme systems, a most important point in therapeutics.

Among the still more complex Chlamydozoaceae there is only one organism of interest to the dermatologist, that of lymphogranuloma venereum. These organisms apparently do have rudimentary enzyme systems and therefore present a different type of treatment problem.

Since the viruses cannot, like the bacteria or fungi, be classified by cultural characteristics or metabolic activities, we fall back upon the rather unsatisfactory method of classification by the size of the infectious agent.

As in most laboratory science, obtaining an absolutely pure sample of the material under study is of vital importance to the investigator. This applies in force to virology. Many of the promising new technical advances in developing new therapeutic methods in this field depend upon purification as the first step. Without going into detail it should be pointed out that two enormous obstacles have had to be overcome in developing purification techniques. The first stems from the fact that (unlike bacteria for example) the very small size of virus particles puts them in the same size range as that of the host material from which they must be separated. The second was the matter of adsorption or adhesion between the host tissue and the virus particle under study. Suffice to say that overcoming these and other difficulties held up progress in solving therapeutic problems in virology for many years.

In order to understand the skin viruses we must observe briefly the unique method by which the viruses propagate. The theory which follows has been worked out and tested by investigators using the light and electron microscope and by biochemical techniques.

Viruses do not propagate by cell division or fission like bacteria or other organisms or cells in nature. The virus elementary

body apparently enters the host cell and, instead of immediately killing it, induces the host cell to stop its own growth and reproductive processes and go into the business of making virus material, following the pattern of the invading elementary body In so doing the virus particle does one of the great salesmanship jobs of all time, for in effect, it makes the host cell commit suicide and indeed fratricide, for as soon as the host factory cell is full of new virus particles, it "bursts, and the newly manu factured virus particles are now free to invade brother host cells and repeat the cycle. The foregoing description is based on observations made on several viruses such as bacteriophage and that of vaccinia and, although not proved for many other viruses, may be tentatively accepted by the nontechnical observer Since certain methods of treatment of infectious diseases attack the reproductive link, it will be seen that the unique method of viral multiplication introduces unique therapeutic problems.

A few words about the interference phenomenon are in order at this point. Long ago it was found that if an animal were injected simultaneously with a dose of two related strains of virus, each of which would ordinarily be lethal, the animal became ill but did not die. This has been called the interference phenomenon and is now an established fact. The mechanism of this event is not known, but several theories are being studied at present. These include the possibility of competition among the two viruses for a key enzyme or essential metabolite, so that neither virus is satisfied completely The possibilities of using the interference phenomenon as a therapeutic device are obvious and are being studied at the present time

GENERAL THERAPEUTICS

The brilliant results achieved with the antibiotics in the treat ment of bacterial infections naturally suggested their possible usefulness in attacking the viruses. With a few notable exceptions (lymphogranuloma venereum) it can be clearly stated that specific treatment of viral infections of the skin with antibiotics has been unsuccessful. Used as an adjunct to control secondary bacterial invasion, they have a definite place in the therapeutic

regimen. It is unfortunate that early uncontrolled reports of specific therapeutic success have given a lasting impression to many physicians that certain antibiotics have specific antiviral effects. Even today many patients are being exposed to the potentially dangerous side effects of useless chemotherapy. Why are these new medications ineffective in the virus diseases? Again, the intimate relationship between the parasite and its host probably supplies the answer. If we remember that the virus is actually being manufactured by the host cell, the difficulty of stopping this process without simultaneously injuring the host will be apparent.

The outlook, however, is not as gloomy as one might suppose. The work of certain investigators in attempting to "feed" the virus producing cells incomplete raw materials (metabolite analogs) thus producing defective virus particles, is most promising. In addition a large number of new drugs such as Atabrine, thiouracil, and pneumonia polysaccharide have been found to inhibit in vivo virus proliferation. An interesting summary of these studies has been prepared by Horsfall and should be read by anyone interested in the treatment of skin virus disease [3].

The induction of passive immunity to certain virus diseases suggests the use of immune serums as a form of treatment. By and large such attempts have failed. For the answer to this failure we return again to the bête noire of the virologist, the unique intracellular position of the virus. In order for the immune serum to inactivate the virus it must contact it. The virus located in the intracellular stronghold is apparently unaffected by introduction of antibodies into the host after symptoms have appeared. *This has been ably demonstrated by Andrews' time* sequence experiments in rabbits, which demonstrate that when the virus has had time to gain the intracellular position, passive immunization therapy is useless. The use of gamma globulin therapy in patients with hypo- or agammaglobulinemia is of course a special situation in which such treatment may be beneficial.

The use of steroids for their antiinflammatory effect is established. One might suppose that they would be of value in the

treatment of viral entities. This has, in general, proved to be not so. In fact they have been found in some instances to be deleterious rather than helpful in therapy [4]

HERPES SIMPLEX

The clinical disorders caused by the virus of this disease are among the most common which affect mankind. Perhaps the disease should be renamed herpes complex because of the varied and interesting syndromes which result from the attacks of this peculiar virus. In order to approach the treatment of these syndromes one must understand the host parasite relationship. The most important fact to keep in mind is that the clinical manifestations are divided into two types (1) the primary types occurring in patients without serum neutralizing antibodies and (2) the recurrent types occurring in patients with demonstrable serum antibodies. I have called this "the paradox of herpes simplex, for unlike other infectious diseases the patient with recurrent attacks of the disease almost always demonstrates a high neutralizing antibody titer to this virus. The importance of this point will be seen later in the discussion of the treatment of recurrent herpes labialis. Now let us turn to the treatment of individual diseases caused by the herpes virus.

Acute Gingivostomatitis. This disease is seen most often by pediatricians rather than dermatologists. It is of interest because this is the most common of all the primary types of herpes simplex and represents the usual cause of the high neutralizing antibody titer found in the majority of healthy adults. This disease is usually mild and is seen clinically as an ulcerating gingivostomatitis in a young child with accompanying regional lymphadenopathy and general mild toxicity It is diagnosed by isolation of the virus from the patient's saliva or a rising titer of serum neutralizing antibodies. The major therapeutic problem which might arise is the maintenance of proper fluid and electrolytic balance in an infant who may not be able to take fluids by mouth because of the local inflammation. Otherwise, symptomatic treating will suffice. Recovery nearly always takes place in a week or 10 days.

Acute Vulvovaginitis. This is a primary type similar in all respects to the above condition. It is an acute inflammatory disease with multiple small tender local ulcerations. Treatment is entirely symptomatic.

Inoculation Herpes. This is an unusual condition in which the virus is implanted in the skin through an abrasion (traumatic herpes) The usual source is from the lesions of an adult who kisses the child's abrasion "to make it well" and instead inoculates the virus. The symptoms are a mild vesicular inflammatory outbreak at the site. Symptomatic therapy with 0.1% neomycin wet dressings in the acute phase and later neomycin ointment will usually prevent bacterial invasion and thus hasten the healing process.

Eczema Herpeticum. Formerly known as Kaposi's varicelliform eruption, this disorder is to the dermatologist the most important primary herpetic infection. The disease represents the inoculation of herpes virus into the skin of a patient with a preexisting eczematous eruption, most often atopic dermatitis. It must be suspected particularly when a person with atopic dermatitis suddenly develops a flare-up of the dermatosis with vesiculation, fever and toxic manifestations. Many mild attacks of eczema herpeticum undoubtedly go unrecognized because of the confusion of having one disease superimposed upon another Diagnosis can be established immediately by the cytologic smear technique [5] or with less dispatch, by isolation of the virus in the chick embryo Serologic diagnosis comes too late to be of value in management. The therapist should take into account that there is an appreciable mortality rate associated with this disease, and hospitalization should be considered. Since there is no specific antiherpetic agent, supportive therapy with particular attention to fluid and electrolyte balance is paramount. The use of gamma globulin injections daily is probably of little value but may be tried, particularly in severe cases.

Antibiotics may be used if secondary bacterial infection is feared, although this is actually a rather unusual occurrence in the author's experience. Cortisone and ACTH are of no value unless there is a complicating encephalitis in which case the

steroids may be of value. The cutaneous lesions require the usual dermatologic antiinflammatory approach with wet dressings in the acute phase, progressing to an ointment as the disease spontaneously clears. It is of interest that in some instances the underlying dermatosis is temporarily much improved following an attack of eczema herpeticum.

Recurrent Herpes Labialis. Under this heading one can include herpes progenitalis, and recurrent herpetic lesions in other areas such as the buttocks. The local treatment of the acute eruption usually resolves into dermatologic wet dressings with 0.1% neomycin solution, proceeding to the application of drying shake lotions as the acute inflammation subsides. The use of local x-ray therapy seems to have no particular rationale, but many experienced dermatologists believe in its efficacy and therefore it is accepted on this basis. The occasional severe case with stomatitis and ulceration of the lips and mouth may present a difficult problem. Sedation, measures to relieve the pain of ulcerations such as topical anesthetic lozenges become important in such instances.

Prevention of recurrences of herpes labialis is one of the commonest therapeutic problems which confronts the dermatologist. The most commonly used method is that of repeated smallpox vaccinations between attacks. This approach is scientifically unsound. First, it has been demonstrated that there is no cross immunity between herpes simplex and vaccinia (smallpox vaccine). Second, even if this procedure *were* to increase the circulating herpes antibody titer it is hard to see how this would help the patient, since the persons afflicted with recurrent herpes are the very ones who already possess a high neutralizing antibody titer. Keeping these facts in mind one can say that this procedure is irrational. Strangely however it is a quite successful method of treatment in many instances. In fact, I use it routinely in preventing the recurrence of herpes simplex. The mode of action of this bizarre form of therapy is unknown but possibly lies in the field of suggestive therapy since there have been studies showing a strong relationship between emotional upset and attacks of herpes labialis.

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cannot penetrate the cell membrane and come into contact with the virus itself In addition, the published reports of success with this mode of therapy have been most unconvincing. A relation ship between herpes zoster and the lymphoblastomas has been noted statistically for years, and a complete blood count should therefore be performed on a patient. The management of the cutaneous manifestations of herpes zoster boils down to local dermatologic management, control of pain, and avoidance of contact between the patient and children without a history of chickenpox.

The treatment of postherpetic pain, which is apparently a result of chronic inflammation in and around the nerve root, usually evolves upon the dermatologist. This unpleasant complication is seen most commonly in the elderly patient. Although many remedies have been suggested, no one treatment or combination of treatments has been found successful in any large percentage of cases. Fortunately the symptoms subside spontaneously after a prolonged period in most instances. In the meantime, the patient may benefit from the use of analgesics, pressure dressings to the skin, and cold applications. The treat ment of herpes zoster and its complications is one of the outstand ing opportunities in the field of dermatology for the physician to display his virtuosity in the relief of symptoms while awaiting spontaneous recovery I wish to state that no criticism is intended of those who employ some of the irrational methods of treatment used in this and many other viral diseases of the skin, as long as the physician himself is aware of their lack of specific effect on the virus and is using them as psychotherapeutic aids in prac ticing the art of medicine.

VACCINIA

There are several important syndromes caused by infection with this organism. These will be considered in their order of importance.

Eczema Vaccinatum. The situation in eczema vaccinatum is similar in many respects to the previously discussed eczema herpeticum, except that in this instance the agent is the virus of

vaccinia rather than herpes simplex. In most cases the history reveals that a patient with some form of eczematous dermatitis (usually atopic dermatitis) has either been recently vaccinated against smallpox or has been in close contact with another person who has. The vaccinia virus spreads rapidly from the inoculation site to involve most or all of the eczematous area of the skin, and a severe toxic disease with hundreds or thousands of vaccinia lesions scattered over the body results. At this point I would like to emphasize that it is an extremely risky and pointless practice to vaccinate any person with an active eczematous eruption. Smallpox is now practically extinct in this country. Thus, to expose a patient to a possibly fatal illness with virtually no possible benefit from the procedure is entirely illogical and should be condemned.

The patient with moderate or severe eczema vaccinatum presents a pathetic picture. The body surface including the palms, soles and even the mucous membranes, is studded with papules, pustules, and crusted lesions in varying stages of development and regression. Fever, malaise, headache, chills, and other symptoms of toxicity are severe.

There is no specific antivaccinal agent at this time [7]. Many patients need hospitalization because of the expert nursing care required. There is no need to isolate these patients, as is frequently done because of the frightening clinical picture. The disease is not contagious to persons who have been vaccinated adequately. The proper dermatologic care changes with the course of the eruption. In the acute phase, wet dressings and shake lotions are important, later progressing to a soothing liniment as the lesions heal. Water and electrolyte balance must be properly maintained, and a specialist in this field should be consulted. Control of the acute toxic symptoms such as fever and headache are treated in the usual fashion. Signs and symptoms of encephalitis should be watched for, although this is an unusual complication. Secondary infection is a rarity in my experience, but if suspected, appropriate antibiotics should of course be given.

In the past few years Dr. Kempe, of the University of Colorado

Medical School has maintained a supply of vaccinia hyperim mune globulin on hand for use in the treatment of vaccinia syndromes. The material may be of great value *early* in the development of this disease and may be obtained with dispatch from Dr. Kempe, using air freight for transportation.

Generalized Vaccinia. This is a disease similar in all respects to the foregoing except that the patient has no preexisting eczema. The virus apparently spreads from a smallpox vaccina tion via the blood stream, and lesions appear on the skin in disseminated form. The treatment is the same as in eczema vac cinatum.

The mortality rate in both of the above diseases has been high in the past, but, with proper attention to fluid and electrolyte balance and modern nursing care and the use of hyperimmune globulin, this death rate has been greatly reduced.

Gangrenous Vaccinia. This is a rare complication most often seen in persons with agammaglobulinemia. In this disease the vaccination site enlarges tremendously and miliary lesions may arise on other portions of the body They may become necrotic and erosive and present a frightening picture. Treatment is the same as in the other vaccinial syndromes with of course par ticular emphasis on the use of hyperimmune human globulin.

WARTS

All warts are caused by the same virus. The difference in clin ical appearance of the different types such as plantar warts and verrucae acuminata is due to variation in the area of skin in-volved and age group etc. The most common types of verrucae will be discussed separately

Verruca Vulgaris. The common wart is most commonly seen in children but may appear at any age. The usual technique of dealing with warts involves destruction by some modality such as fulguration, cauterization, or the use of a strong acid. Any of these methods may be used with good results. The experienced dermatologist varies the therapeutic attack depending on the size number and location of the warts and the age of the patient. The most common method is electrodesiccation. This is effecti e a

the majority of instances, and the recurrence rate is low However the method requires the injection of local anesthetic with the attendant pain and possible risk of allergic sensitization. Scarring is nearly always a sequela. If the lesions are many the treatment is time-consuming and unpleasant for the patient. For single large warts fulguration is the method of choice. The weekly application of monochloroacetic acid is preferable when there are many lesions present, or when the use of a local anesthetic is contraindicated. Scarring occurs with this method but is usually less than with fulguration.

Suggestion therapy is frequently successful in children, less often in adults. Professional wart charmers are practicing their art even today and claim cure rates as high as 60 to 70 per cent. No controlled reports are available, but there is no question but that therapeutic suggestion is successful in many instances [8] The usual method is to paint the lesions with a dye such as gentian violet and suggest strongly to the patient that within a week *they will dry up and fall off* *Excision of warts is seldom* practiced any more and is the least appropriate. The technique is cumbersome and expensive, and the recurrence rate is high. Freezing the warts with liquid nitrogen or solid carbon dioxide is often successful.

Injection of bismuth subsalicylate intramuscularly at weekly intervals has been suggested for cases where destruction is not feasible. The site and mode of action of bismuth is not definitely known, but occasionally severe outbreaks of warts can be controlled with this drug

Verruca Plana. The treatment of verrucae planae depends on the location and number of lesions. Destructive techniques (which usually produce some degree of scarring) would be out of place in cosmetic areas On the other hand desiccation or the application of acid is perfectly appropriate in the treatment of a *few* lesions on the hands or trunk.

This variety of wart seems to be particularly susceptible to treatment by suggestion, and this approach is usually tried first. If there is no response, intramuscular injection at weekly intervals for several months of bismuth subsalicylate is worth a trial.

Most dermatologists have seen spectacular instances of clearing of multiple verrucae almost overnight as a result of the injection of this drug. The exact mode of action of this medication is unknown, and since it may be only a form of suggestion, I always try to reinforce its activity by combining it with a strong suggestive approach.

Dermatologic fractionated low dosage x ray therapy is sometimes successful. Some clinicians consider this to be a form of psychotherapy X radiation in the dosages ordinarily used has no specific lethal action on the virus itself

Condyloma Acuminatum. Condylomata acuminata are merely warts growing in a moist area or on a mucous membrane. The vulva, anus, and penis are the most common sites, but lesions have been described in the eye, mouth, and so on. The treatment of choice is application of podophyllin, a cellular poison, which is usually applied in a 25% alcoholic solution at weekly intervals until the lesions are eradicated. The material is very irritating and cannot be used in the eyes or in other areas when an inflammatory effect would be harmful [9] The other methods of treatment such as fulguration and applications of acid may be used to advantage in resistant cases.

Verruca Plantaris. Plantar warts frequently present a unique and irksome therapeutic problem. There are literally dozens of proposed treatments for this condition, any of which may be successful. My personal choice is the application of monochloroacetic acid followed a week later by curettage of the dead wart material and reapplication of the acid, repeating this process until the verruca is eliminated. The method has the disadvantage of being time-consuming and occasionally somewhat painful. The advantages, however are the safety simplicity and absence of painful scar formation after removal of the lesion. I do not use x-rays because of the relatively high dosage needed to effect a cure. Surgery on the bottom of the foot is an unattractive procedure for many reasons, such as the prolonged postoperative bed rest required and the possibility of developing a painful scar at the site. Most surgeons rightly refuse to handle these patients except in special circumstances.

Some mention must be made of the use of the heat killed, *phenolized vaccine injections* made from ground-up wart material. This method proposed by Biberstein has never been subjected to adequate controlled clinical investigation [10] In spite of this, in the stubborn or unusual case of any type of verruca the method is worth a try I have seen a case of multiple plantar warts of several decades duration, which had resisted practically every known method of treatment, respond completely and dramatically to vaccine injections. Other dermatologists have had similar experiences.

Molluscum Contagiosum. This disease is caused by the largest of the skin viruses and is characterized by the appearance on the skin of multiple asymptomatic seed pearl nodules. The lesions vary in size from pin point to over a centimeter in diameter

For the usual case simple destruction by fulguration, application of acid locally or excision will suffice The method of choice is curettage with an instrument just slightly larger than the lesion It is painless, safe, and simple. Once all the lesions have been removed recurrence is unlikely

One might suppose from the large size of this virus that systemic or local antibiotic therapy might be effective. Unfortunately this has not proved to be the case.

CONCLUSION

In this discussion I have attempted to give a skeleton background of basic virology which was used as a springboard for the consideration of treatment of the individual viral entities. The practical discussion of treatment methods has been brief because of the lack of specific weapons against these agents I have for the most part presented only my own approach to the therapy of each disease.

There is no question but that in the near future striking improvements in treatment methods will be forthcoming. Until that time one must rely on the time-tested approach to the therapy of viral disease

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Robert H Zeilenga

24

SYNDROMES RELATED TO BACTERIAL ALLERGY AND HYPERSENSITIVITY

Bacterial infections are capable of producing many types of cutaneous responses. Numerous syndromes have been described based on tissue reaction to the bacterial infection. For a better understanding of the pathogenesis of the various syndromes, the following definitions are given *Allergy* is an acquired specific alteration in the capacity to react brought about through the interaction of an antigen with its specific antibody The sensitization is developed as a result of exposure, and the reaction is based on an antigen-antibody combination. *Hypersensitivity* is an exaggerated response and is considered to be nonallergic with no antibody mechanism.

SYNDROMES SPECIFICALLY ATTRIBUTED TO BACTERIAL ALLERGY

Tuberculosis and leprosy are two diseases which can produce allergic manifestations. The reactions produced are in the form of "ids" and are due to sensitization arising from an active infection. No bacilli are found in the tuberculids. Leprids may contain few demonstrable bacilli. According to Pillsbury, Shelley and Kligman [1] the following criteria are necessary for the

diagnosis of tuberculids (1) an active tuberculous focus, (2) a positive reaction to tuberculin test, (3) lesions which are clinically typical of one of the validated types of tuberculid, (4) a tuberculoid histologic structure.

Tuberculids

Tuberculids are divided into two types, the papular and the nodular or granulomatous, forms [1]

Papular Forms. LUPUS MILIARIS DISSEMINATUS FACIEI. Adults are chiefly affected with this form. The lesions consist of discrete, soft, red, slightly elevated papules which are limited to the face. The papules may appear in crops and are often grouped around the eyelids, cheeks, and the angles of the mouth.

PAPULONECROTIC TUBERCULID This condition occurs most commonly in young adults between twenty and thirty years of age [2] The lesions appear as crops of deep-seated, colorless to brownish red, painless papules which may form pustules in the center Central necrosis of the papule produces an ulceration which heals to form a depressed scar The lesions may occur on the face hands, and trunk. On the extremities symmetrical distribution is found.

LICHEN SCROFULOSORUM. This disorder is seen most frequently in children. The disease is characterized by grouped, lichenoid, small, flat-topped papules which occur chiefly on the trunk. The color of the lesions vary from flesh color to vivid red. At first the lesions are isolated, and later they become grouped into round patches. The lesions may persist for months, and involution is accompanied by slight desquamation, but no cicatrices are formed [3]

Granulomatous, Nodular Forms. ERYTHEMA INDURATUM. This disease is a chronic, recurring symmetrical disorder involving the calves of the legs, predominately in young women. The lesions first appear as deep subcutaneous nodules which later involve the overlying skin to form bluish red, slightly tender plaques. These plaques may vary in size from 1 to 4 cm in diameter They undergo necrosis to form ulcers which heal slowly Atrophic depressed scars are produced.

There is no complete agreement on the exact cause of erythema induratum. Becker and Obermayer [2] state that tuberculosis of internal organs can be demonstrated in about two-thirds of the patients. Pillsbury et al. [1] are of the opinion that a primary focus of tuberculosis is rare in erythema induratum. They state that most of the patients with this syndrome are suffering from some variant of nodular vasculitis, the cause of which is usually undeterminable.

The treatment of tuberculids is directed toward the eradication of the primary focus. The recent therapeutic drugs advised in the management include isonicotinic acid hydrazide, streptomycin and para-aminosalicylic acid singly and in combinations.

Leprids

Leprids are the lesions of the tuberculoid type of leprosy. It is difficult or impossible to recover bacilli from the lesions, and the clinical manifestations tend to be limited [1]. The characteristic cutaneous eruption consists of oval or irregular brownish, sharply defined macules which range from 3 to 10 cm in diameter and are distributed over the limbs and trunk [4]. The lesions become anesthetic. The lepromin skin test is positive. The course is chronic. Treatment consists of various sulfones, streptomycin and sodium *p*-aminosalicylate.

SYNDROMES OF UNKNOWN EXACT CAUSES

In most of the following syndromes the various clinical manifestations appear to be the result of vascular damage. The vascular involvement is considered by many authors to be a sensitivity reaction to bacterial infections. In addition to the suggested bacterial pathogenesis, multiple causative agents such as viral or mycotic infections, foods, and also drugs have been listed as causes of some of the syndromes.

Polyarteritis Nodosa

Classical polyarteritis nodosa, originally described as periarteritis nodosa by Kussmaul and Maier in 1866, is one of the better known of the group of vascular diseases which have been

considered to be manifestations of hypersensitivity The portions of the vascular system that are primarily involved are the small arteries and arterioles. The veins are less commonly affected. There is widespread distribution of the vascular lesions, and the clinical manifestations are dependent on the organs involved.

The skin is involved in about 25 per cent of the cases of poly arteritis nodosa [5] The cutaneous manifestations consist of polymorphic exanthemata, urticaria, vesicles, ecchymosis and gangrene, subcutaneous nodules, edema, livedo reticularis, and ulceration [6] Lyell and Church [6] consider the subcutaneous nodule to be the essential lesion.

The nodules vary in size from a pea to a hazel nut, appear in crops, may be transient, and tend to be grouped along the course of the artery The overlying skin may be unchanged, reddened, thinned, and glistening, or may ulcerate.

Because of the involvement of many organs, bizarre symptoms may be present. Systemic signs of fever leukocytosis, and anemia are generally present. Involvement of the gastrointestinal and genitourinary systems occurs in practically every instance [7]

The pathologic lesions represent a panarteritis. Lever [8] lists four stages on a histologic basis. In the first stage, the intima and media undergo necrosis in segments, and only portions of the vessel are involved. Aneurysms may form in areas of seg mental necrosis. The second stage shows acute inflammation and the lumen and adventitia are infiltrated with polymorphonuclear leukocytes, eosinophiles, lymphocytes, and plasma cells The for mation of granulation tissue is the third stage, and this leads to partial or total occlusion of the lumen. In the fourth stage, the destroyed vascular wall is replaced by scar tissue. The lumen may be reduced in size or show obliteration or recanalization

The exact cause of polyarteritis nodosa is unknown. Sutton [4] considers it to represent an allergic reaction of the small arteries to a variety of antigens. Lever [8] considers the disease to be a manifestation of hypersensitivity although the cause may not be apparent in most cases. Rose Littmann, and Houghton [7] from their examination of the literature concluded that the causes of polyarteritis nodosa are probably diverse and that sensiti ity to

grade fever arthralgia, malaise, and headache may accompany the eruption.

The histologic findings are characteristic. The constant outstanding abnormality is a severe vasculitis of the arterioles and capillaries in the cutis. Swelling and dissociation of the endothelial cells with fibrinoid change of the vascular wall and the adjoining connective tissue occur [18] The inflammatory infiltrate consists mostly of polymorphonuclear leukocytes. Disintegration of the neutrophils produces characteristic fragmentations.

In considering the cause of allergic cutaneous vasculitis, most authors agree to an allergic pathogenesis Ruiter [19] is of the opinion that foreign proteins, drugs and especially bacteria are possible antigens in this particular type of allergy Gougerot and Duperrat [20] considered the skin to be sensitized to bacteria, and that the lesions resulted from the reactions produced by bacterial emboli arriving at the skin. Marshall and Pepler [21] are of the opinion that a microbic allergen is implicated.

Many types of treatment have been advocated Removal of foci of infection, antihistamines, antibiotics, and vaccines have produced only equivocal results [21] Temporary improvement has been reported after the use of corticotropin and cortisone [21 23]

Purpura

Purpura is a disorder characterized by hemorrhage into the skin or mucous membranes. The most common lesions of purpura are petechiae which are circumscribed, punctate, superficial macules 1 to 5 mm in size. Larger macular lesions, often irregular in shape are called ecchymoses. If the superficial lesions are striate or linear they are designated as vibices. Deeper more diffuse accumulations are known as suffusions or bruises. Purpuric lesions appear suddenly do not fade under pressure, are bright red in color if superficial, and bluish if deeper As the blood pigment is absorbed in older lesions, the color changes to purple, brown, and yellow before fading.

Many types of infections may be complicated by purpura. It appears to bear no relationship to the severity of the primary

disease and may complicate mild or severe infections [24] An asymptomatic latent period between the onset of the infection and the appearance of the purpura may be present. This period between the infection and the development of purpura indicates the time required for the development of hypersensitivity [1] Thrombocytopenia is usually present. A rare clinical syndrome known as purpura fulminans may occur as a complication of infections caused by *Neisseria meningitidis*, *Pseudomonas aeruginosa* and *Streptococcus hemolyticus*. It is characterized by rapid, progressive symmetrical subcutaneous ecchymoses High fever intense systemic symptoms, and death usually occur within a few days after the onset [25]

Another rare, overwhelming disorder with fulminating purpuric manifestations but a normal platelet count is the Waterhouse-Friderichsen syndrome. It accompanies meningococcemia and is characterized by a sudden onset with high fever headache, vomiting, and widespread symmetrical ecchymoses Hemorrhage into the adrenal glands produces generalized circulatory collapse, and the patient generally succumbs within 12 to 24 hours

The Henoch-Schönlein syndrome, also known as allergic or anaphylactoid purpura, is a nonthrombocytopenic disorder The disease is usually seen in children, and males are more commonly affected The cutaneous lesions begin as symmetrically distributed, erythematous papules which appear on the lower portion of the back, buttocks, and lower extremities. Central hemorrhage into the papule occurs. Petechiae, ecchymoses, and pruritic urticarial lesions also may occur The cutaneous manifestations of the Henoch Schönlein syndrome may be minor or even absent. Fever anorexia, visceral symptoms of abdominal pain, joint symptoms of swelling, tenderness, and pain more commonly dominate the picture [24]

Rostenberg [34] considers the purpura of infection, including purpura fulminans and the Waterhouse-Friderichsen syndrome, possibly to develop by a Shwartzman mechanism. The cause of the Henoch-Schonlein syndrome is uncertain. It has been considered as a sensitivity to tuberculosis [26] streptococcal infections [27 28] and foods [29] Dameshek [30] considers Henoch-

Schönlein purpura to be an allergic or immunoallergic disturbance and describes this syndrome as an immunovascular disease. Ackroyd [24] in his review of the extensive literature has concluded that, although the condition is widely believed to be a manifestation of allergy this is entirely unproved except for the very small proportion of cases which appear definitely to be due to hypersensitivity to food.

The treatment of the previously discussed purpuras is directed toward the cause if known. Infections are treated with the appropriate antibiotic or chemotherapeutic agent transfusions are given when indicated and offending allergens are eliminated. Since the advent of corticotropin and cortisone, the hemorrhagic manifestations can often be promptly controlled [29, 31, 32] However Wintrobe [33] is of the opinion that the results of treat ment with ACTH or cortisone have been equivocal or disappoint ing.

Pyoderma Gangrenosum

Pyoderma gangrenosum is a chronic, recurrent, ulcerative dis order of the skin which often occurs in association with a septic focus.

In 1930 Brunsting et al. [35] suggested the name for this syndrome and reported the association of the cutaneous ulcers with ulcerative colitis and also empyema. The initial lesion may follow a traumatic break in the skin or begin in a draining wound. A painful serpiginous ulcer with a red, granulating base covered with a foul-smelling, purulent exudate is formed. The margin may be undermined and show an outer erythematous halo inside of which is a swollen purplish collar [36] Multiple ulcers usually develop, and they may become quite extensive. Meleney's chronic undermining ulcer and progressive bacterial synergistic gangrene are considered to be the same entity [36 37]

Many different bacteria have been cultured from the ulcers, and there is no general agreement as to the extent to which bac terial parasitism is directly responsible for the cutaneous lesions [4] Rostenberg [34] is of the opinion that a Shwartzman phenomenon is operative in producing the cutaneous ulcerations

Treatment of pyoderma gangrenosum has included antibiotics [38, 39] gamma globulin [40] surgery [41 42] and cortisone [38] The most satisfactory results have been obtained by surgical excision and grafting and also by the administration of cortisone [38]

Erythema Nodosum

Erythema nodosum is a significant clinical entity characterized by the appearance of multiple, bilateral, painful transient nodules involving the skin and subcutaneous tissues.

The nodules appear in crops, mainly on the legs, and may be preceded by constitutional symptoms of fever malaise, and joint pains. The lesions are round or oval, soft or firm, red or purple slightly elevated nodules which do not suppurate. Young adult female patients are most frequently affected in this disorder Spontaneous disappearance occurs in 2 or 3 weeks.

The histologic changes are most pronounced in the subcutaneous tissue which shows a scattered infiltrate consisting of neutrophiles and lymphocytes. The veins show invasion of the vascular walls by the inflammatory infiltrate and marked endothelial proliferation [8] Arterial changes similar to those of polyarteritis nodosa may also be found [43]

Erythema nodosum is considered to be a manifestation of hypersensitivity [44] It may follow bacterial infections, particularly of streptococcic origin, and also fungal and viral diseases [45] Drugs which most commonly cause erythema nodosum are the sulfonamides, iodides, and bromides.

Treatment is directed toward the underlying disease The syndrome is self-limited. Corticotropin and cortisone may be beneficial, but they are not advised because of the possibility of spreading an underlying infection [1 4]

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Rudolf L. Baer **25**

STEROIDS IN DERMATOLOGY

THE ADVENT OF NEW DRUGS often has dermatologic consequences in one form or another Some new drugs assume importance from the dermatologist's viewpoint mainly because they cause an excessive incidence of allergic drug eruptions. Others find important dermatologic applications in addition to their other uses. Whereas formerly impetigo, furunculosis, carbuncles sweat gland abscesses, etc., were seen daily in dermatologic practice and often presented difficult therapeutic problems, they have now become much less common and are easily managed largely because of the effects of the antibiotics. Similarly the development of the antihistamines has had a profound effect on the management of urticarial and pruritic eruptions.

However probably the most significant single advance ever made in dermatologic topical and systemic therapy has been the advent of ACTH and of cortisone and its analogs. At the outset let me state that these hormonal substances, neither when applied topically nor when given systemically *cure* any dermatoses. They do, however suppress and alleviate a considerable number of skin diseases, including harmless and serious and acute and chronic dermatoses and diseases which as far as one can tell

apparently are based on entirely different causative mechanisms.

Much has already been learned about the effects of cortisone and related compounds on the skin, but the available information still is not yet sufficiently complete to explain the very striking action of these drugs in a great variety of cutaneous diseases. Some of the effects of cortisone take place at a cellular level in the skin itself, while others are brought about via an action on other tissues and organs.

One of the most important results in the skin of cortisone administration is the depression of connective tissue reactivity This alone probably accounts for many of the clinical benefits in cutaneous diseases. There is interference with the formation of *fibroblasts, of ground substance, and of granulation tissue. Other* effects in the cutis are impaired vascularization and inhibited inflammation The epidermis on the other hand is not markedly influenced by ACTH and cortisone, the only notable effect being an excessive keratin ring formation at the follicular orifice which may lead to the development of acne-like lesions.

Some enzyme systems in the skin are affected by ACTH and cortisone Hyaluronidase activity for example, is strongly impaired, an action which lessens the spreading rate of bacterial products, fungous products, and other substances in the skin

The blood flow in the peripheral capillaries tends to be accelerated, and consequently the skin temperature tends to become elevated. This is in contrast to the antipyretic effects of ACTH and cortisone in febrile diseases. Delivery of sweat to the skin surface tends to be increased, but that of sebum is decreased, a fact which explains the nonseborrheic dry skin of patients with ACTH and cortisone-produced acne

With respect to cutaneous reactivity it has been observed that cortisone administration causes no interference with urticarial responses to allergens or to primary urticariogenic agents such as histamine. Allergic eczematous sensitivity often decreases to a very minor degree, the reduction in sensitivity being so slight as not to become manifest in patch tests when standard concentrations of allergens are used. The 48-hour tuberculin-type reaction also often is diminished under the influence of cortisone.

All evidence to date indicates that there is no significant interference with the body's antibody production or with interaction of antigen and antibody in the skin. ACTH and cortisone, however, do interfere with the damaging effect of the products of antigen-antibody interaction on the skin cells.

TOPICAL USE OF HYDROCORTISONE AND ANALOGS

I should first like to take up here the effects of corticosteroids as topical medicaments. Except for a few important additions like the antibiotics and antiscabietics, local therapy in dermatology was fairly well stabilized for several decades. Prior to the development of the corticosteroids there has been no major progress in topical dermatologic therapy since the introduction of coal tar in 1909 by Dind and others. The story is told that Dind's dog had a cutaneous eruption of many years duration. One fine day the dog rolled on a street on which tar was being spread for purposes of paving, and within a very short time thereafter his eruption cleared. This observation (plus the cheapness of coal tar as compared with the previously used wood tars!) stimulated Dind† to study the composition, properties, and clinical effects of coal tar. Compare this chance discovery of the therapeutic value of coal tar with the modern methods of biochemical and clinical investigation which resulted in the discovery of the corticosteroids and their remarkable effects upon topical application.

Cortisone itself is ineffective when applied directly to the skin, apparently because the skin is unable to convert it into the biologically active hydrocortisone. Hydrocortisone on the other hand has such a high degree of biologic efficacy as a topical medicament that generally it has not been surpassed by 9α-fluorohydrocortisone, prednisone, prednisolone and more recently developed analogs which have been under study. Several of these analogs are quantitatively more active than hydrocortisone, i.e.,

I am indebted to Dr. R. Gonin and Dr. J. David Gerver of Lausanne for the information that Dind actually began therapeutic trials with crude coal tar after several of his assistants had seen marmers treat their hands with this substance.

† He called attention to the fact that 1 kg of coal tar costs Swiss centimes (½ American cent according to the present exchange rate).

they exert a comparable effect in smaller concentration, but generally they have not been capable of achieving better results than hydrocortisone. Since preparations containing these other corticosteroids are just as expensive as those with hydrocortisone, I fail to see any real advantage in their routine use.

Though in most instances there is no significant difference in the topical therapeutic efficacy of these various analogs of hydrocortisone, there are exceptional cases where one appears to be more effective than the others. For example, occasionally an eruption which has failed to improve under 1% hydrocortisone ointment will respond to 0.1% 9α-fluorohydrocortisone ointment.

In general, a 1% concentration of hydrocortisone appears to be most suitable for *routine* treatment. However some cases will respond to such small concentrations as ⅛% or even ¼% while others will do much better with a 2.5% or 5% preparation than with a 1% preparation, but these are the exceptions to the rule. Usually two, or at most three, applications daily are sufficient, and additional applications will not bring about greater therapeutic benefits.

Hydrocortisone is colorless and odorless. Preparations containing it therefore are usually not messy and are well accepted by patients. Bandaging is not necessary since very small quantities of cream, ointment, lotion, or other preparation are as a rule sufficient, and these may be gently massaged into the skin without leaving a removable surface film.

Dermatoses Benefiting from Topical Steroid Therapy The following are among those dermatoses which benefit appreciably from topical applications of hydrocortisone and related compounds:

- Atopic dermatitis (in all its phases from infantile eczema to the adult form)
- Eczematous (papulovesicular) eruptions including allergic and nonallergic dermatitis, nummular eczema, winter itch.
- Eczema and eczematous epidermophytids. It should be noted, however that in the hyperacute phase the large vesicular and bullous lesions of eczematous eruptions usually fail to respond.
- Seborrheic dermatitis of the glabrous skin.

Psoriasis (usually only superficial lesions especially on the face and in the anal and genital and inguinal regions)
Pruritus ani and vulvae (especially when associated with signs of inflammation, however some cases respond even though they show no visible inflammatory reaction)
Otitis externa. (A good response is often elicited, no matter whether the underlying eruption is psoriasis seborrheic dermatitis, topic dermatitis, or some other process)
A satisfactory response is produced also in some cases of herpes simplex, pityriasis rosea, dermatitis herpetiformis, senile pruritus, and other dermatoses.

If topical application of hydrocortisone is effective, fading of erythema, decrease of edema and itching, and beginning or advanced involution of the active lesions usually can be observed within a few hours to 48 or at the very most, 96 hours. In general, no beneficial effects should be expected if none has been noted within 96 hours. Similarly the eruption is likely to recur within 1 to 4 days after discontinuation of the treatment unless it has run its course.

Vehicles. It is a well-known fact that the choice of the proper vehicle in topical dermatologic therapy is often equal in importance to the selection of the proper active ingredients. Experience has shown that while in topical therapy with corticosteroids the choice of the proper vehicle is not quite as important, it is nevertheless advisable to follow the conventional principles in selecting the vehicle. In acute processes it is usually best to prescribe hydrocortisone in lotions or nonocclusive and nongreasy creams such as oil in water or water in oil emulsions, carbowax bases can also be used, but in some instances they have proved to be somewhat irritating and drying. For the chronic and torpid lesions ointments of petrolatum or petrolatum and lanolin are often preferable.

In otitis extra hydrocortisone is best used in suspension as ear drops. This form of application encourages dryness in the ear canal and does not interfere with drainage to the outside, as ointments and creams often do.

Topical Combinations. In recent years there has been an increasing tendency to prescribe combinations of hydrocortisone

or its analogs with other topical medicaments. In my opinion this is a move in the right direction and follows the time-honored dermatologic principle of combining several topical medicaments, thus achieving additive or in some instances synergistic therapeutic effects, often without substantially increasing the irritancy or sensitizing capacity of the preparation At the same time *one must object to the routine addition to hydrocortisone* of other medicaments for which there is no indication, especially if such ingredients entail a risk of allergic or other side effects.

For example, there is no reason for routinely combining neomycin with hydrocortisone. Neomycin is a useful topical antibiotic, but it produces a certain incidence of allergic contact sensitizations. Therefore, it increases the risk of side effects without adding to the therapeutic efficacy of hydrocortisone preparations and so is not indicated unless there are good reasons for its use, such as evidence or suspicion of secondary infection with neomycin susceptible organisms. Neomycin or polymyxin B combinations with hydrocortisone are indicated in otitis externa, for example when there is evidence or suspicion of superimposed infection with *Pseudomonas aeruginosa* In patients with eczematous eruptions where it is suspected that pyogenic or other bacteria or fungi may be playing a contributory role, the combination of hydrocortisone with Sterosan, Vioform, or Diodoquin has proved helpful

In the treatment of seborrheic dermatitis or superficial psoriasis the combined use of hydrocortisone with tar and mercury or sulfur makes sense, since the benefits to be achieved with the combination of medicaments are likely to occur more quickly and to be more *striking and longer lasting than those with a preparation* containing hydrocortisone only In eczematous eruptions it appears sometimes desirable to make use of the antiinflammatory effects of hydrocortisone, the antieczematous action of coal tar and the mild bacteriostatic and *fungistatic action of Sterosan,* Vioform, or Diodoquin For example, crude coal tar 1% and hydrocortisone 1% in Sterosan ointment or Vioform ointment is often highly effective in these eruptions

When observing patients who are being treated with preparations containing hydrocortisone in combination with other active medicaments it must be kept in mind that the hydrocortisone may occasionally partially or entirely mask an allergic contact dermatitis due to one of the other ingredients in the combination. This event accounts for some otherwise unexplained severe recurrences or extensions of eruptions after discontinuation of treatment with combined preparations.

Topical medicaments containing corticosteroids alone, however have a remarkable record with respect to a very low incidence of allergenic side effects. After 6 years of prescribing topical hydrocortisone preparations for my patients I have not yet seen, nor have I heard or read of an authenticated case of allergic hypersensitivity to hydrocortisone or its analogs. Those allergic reactions which have occurred because of topical hydrocortisone preparations in each instance have been traced to the vehicle or to other active agents in the medicament.

When hydrocortisone first came into general use as a topical medicament, it was feared that its very vigorous suppressive action on inflammation perhaps would impair the normal defenses of the skin to such an extent as to lead to an excessive incidence of mild or even invasive secondary infections of the cutaneous lesions. In my experience these fears have proved unwarranted I have not noted any increase of pyogenic, fungous, or viral infections in areas treated with hydrocortisone preparations. This holds true even for areas which are especially prone to develop secondary infections such as the genital and anal regions, where infections are likely to occur with *Candida albicans*. On the contrary as was previously noted, in selected cases it is advisable to combine the action of an antibacterial or antifungal medicament with the antiinflammatory action of hydrocortisone to combat an infectious process. Thus monilial eruptions of the genital areas often respond excellently to hydrocortisone 1% in Mycostatin ointment or paronychial infections on the hands to hydrocortisone 1% in an ointment containing Mycostatin and Sterosan, or fungous infections of the feet to hydrocortisone 1% in sulfur salicylic acid ointment.

Systemic Absorption. Much thought has been given to the question of whether or not topical corticosteroid therapy may produce systemic effects. This is a problem of the greatest practical importance, because some cases require that hydrocortisone containing medicaments be used over extensive areas of the body's surface for many months or years. As was to be expected, it has been shown conclusively that some of the corticosteroid applied to the skin or mucous membrane is absorbed, the quantity absorbed probably depending mainly on the concentration of the drug in the preparation, the number and vigorousness of applications, the size of the area treated and, very important, the type of cutaneous change in the affected sites. Again, as one would have expected, there is much more absorption from mucous membranes than from the skin and more from inflamed than from normal skin. Efforts to demonstrate systemic effects from percutaneous absorption of hydrocortisone thus far have failed. This includes failure to reliably demonstrate a drop in circulating eosinophils after application of hydrocortisone to large areas.

Considering the problem purely from the practical viewpoint, to my knowledge there is not a single case on record in which prolonged topical application of hydrocortisone even over large areas has produced systemic effects such as sodium retention, edema, weight gain moon face, hypertrichosis, buffalo hump, hypertension, or diabetes. Hydrocortisone preparations to date have been used extensively for only about 6 years, and naturally the possibility cannot be entirely dismissed that we may yet be presented with some very unpleasant surprises as concerns systemic effects, but so far all the evidence shows that undesirable systemic effects do not follow prolonged use over extensive areas.

In a small percentage of cases treated topically with 9α-fluorohydrocortisone preparations, however systemic side effects have been noted in the form of edema formation due to salt retention It is important that in some cases this has happened even after topical treatment of relatively small areas. This experience with 9α-fluorohydrocortisone should make one wary of accepting new so-called more effective corticosteroids until they have been proved to be free of such systemic action

LOCAL CUTANEOUS INJECTION OF HYDROCORTISONE

Local injection treatment with hydrocortisone is not widely used in dermatologic therapy This is mainly the result of discouraging experiences in most of the dermatoses in which such therapy has been attempted. The number of investigations in this field, however is not as great as would have have been desirable, and it appears possible that more extensive trials may yet turn up additional indications for local cutaneous injection therapy with hydrocortisone. The technique is not difficult. Hydrocortisone suspension 25 mg per ml, as is used also for intra-articular injection, is injected directly into the affected area using a ½- to 1 in., 25-gauge needle attached to a tuberculin syringe. Roughly one injects about 0.3 to 0.5 ml per square inch of skin surface. Among the dermatoses in which a measure of success has been claimed with this treatment are alopecia areata, keloids, lichen chronicus simplex, hypertrophic lichen planus, and small areas of chronic discoid lupus erythematosus.

The effects have been particularly interesting in some cases of alopecia areata, hitherto a disease for which there had been no treatment that was even moderately satisfactory Injections of hydrocortisone suspension into the bald areas every 2 to 3 weeks may lead to a cosmetically significant regrowth of hair The regrowth usually becomes evident 3 weeks after the first injection and persists for many months. There is not yet enough experience with this treatment to permit any definitive statements as to how long the regrown hair will persist, whether if the regrown hair falls again, renewed injections are as effective in producing regrowth as was the first injection, whether some or many cases are permanently cured, whether this treatment is applicable to alopecia totalis etc. Orentreich has shown that the more water soluble newer analogs of hydrocortisone are much less effective with respect to this trichogenic action than the water insoluble hydrocortisone

The treatment of keloids with injection of hydrocortisone suspension in some hands also has produced gratifying results. The injections, which can be given every 1 to 3 weeks, in some cases

are said to cause flattening of the keloid, or their softening action is said to have made the lesions more responsive to treatment with solid carbon dioxide.

It is important to note, however that some local atrophy may follow the intracutaneous injection of hydrocortisone suspension into the glabrous skin, thus giving the skin a slightly depressed and wrinkled appearance.

SYSTEMIC USE OF ACTH AND CORTICOSTEROIDS

There are probably few branches of medicine in which systemic therapy with corticosteroids has found as wide and as varied applications as it has in cutaneous diseases. Here it has proved of great benefit in the suppression of chronic and serious eruptions such as pemphigus and systemic lupus erythematosus, which in the past were usually fatal, in benign but often chronic eruptions as lichen planus, and in benign, acute eruptions like poison ivy dermatitis.

This discussion of the dermatologic uses of systemic therapy with ACTH and cortisone and its analogs will not deal with those phases which, although they have great importance, have no specific dermatologic aspects. Thus I shall omit consideration of the relative merits of ACTH and the various corticosteroids, of combined treatment with ACTH and cortisone, and of the medical contraindications to treatment. With certain exceptions no one compound has been found to be generally more effective in the treatment of dermatoses than the others. The side effects which may occur the tests which must be done to detect them, and the measures which should be taken to prevent or counteract them also are not different in dermatologic management than in noncutaneous diseases.

As in Cushing's syndrome hirsutism occurs in some patients. Striae also are seen but appear to be strikingly less common in patients treated with corticosteroids than in Cushing's disease Then there are the acneform eruptions. These can readily be differentiated from acne vulgaris, since the lesions are smaller more monomorph, and less pustular and are usually located in dry nonseborrheic skin. Another cutaneous side effect of ACTH

and corticosteroid therapy is purpura and excessive bruising. Hyperpigmentation in areas of healed cutaneous lesions is not uncommon. This is probably attributable to small amounts of melanocyte stimulating hormone in ACTH and perhaps also due to an effect on the tyrosinase-sulfhydryl complex which is involved in melanin pigmentation.

The principal purposes of systemic corticosteroid therapy in dermatology are the suppression of the presenting eruption, which in the serious dermatoses also amounts to prolongation of life, and alleviation of subjective complaints, usually itching. The dosages necessary to suppress the eruption and then to maintain the suppression vary widely in different skin diseases and in different patients. In general it is always advisable to start with a dose of corticosteroid sufficient to suppress completely the active cutaneous lesions as well as the systemic manifestations, if any and then gradually to diminish this dose until a maintenance dose has been established or in acute benign eruptions, until the dermatosis has run its course. Since prednisone is at present the most widely used compound all questions of dosage will be discussed in terms of this drug. The average suppressive dose for many dermatologic cases is 40 to 60 mg of prednisone, although some eruptions can be suppressed with 30 mg or less. On the other hand desperately ill patients suffering from pemphigus or lupus erythematosus may on occasion require up to 400 mg of prednisone daily for initial suppression of the lesions.

As far as the maintenance dose is concerned, quantities vary from case to case and to some extent depend on the intentions of the treating physician. In many a patient with atopic dermatitis a maintenance dose of 5 to 15 mg of prednisone per day proves adequate, while in patients with pemphigus 30 to 40 mg of prednisone per day may be required and may have to be continued over a period of months or even years.

Sometimes it may be desirable or necessary to base the maintenance dose on complete suppression of the eruption. At other times the physician may decide that it is neither essential nor desirable to maintain complete suppression. There may be medi

cal reasons which make it impotrant to keep the maintenance dosage at the absolute minimum. Or simultaneously with corticosteroid medication one may wish to evaluate the efficacy of various forms of topical therapy or of other systemic therapy. This can be done while a patient's eruption is only partially suppressed with corticosteroids but not during periods of complete suppression.

Rather than list all the dermatoses in which systemic corticosteroid therapy has been utilized with some measure of success, I shall discuss here only a few selected dermatoses, and the effects of this therapy upon them.

Eczematous Conditions. Excellent results are obtained with regularity in eczematous eruptions, including allergic and nonallergic contact dermatitis, nummular eczema and winter itch eczema. Provided the dose is adequate the results are especially striking in allergic contact dermatitis. Not only can active lesions and itching be suppressed, but the appearance of new lesions can be prevented, something that could never be achieved with any previously available therapy. In my opinion, corticosteroids are not indicated for the routine management of acute or subacute allergic contact dermatitis: their administration should be restricted to cases where the eruption is so severe and extensive as to be incapacitating or where unusual extraneous circumstances require that the eruption be cleared by all available means. Since the allergic skin's capacity to respond with positive reactions to patch tests with standard concentrations of allergens generally is unimpaired during administration of corticosteroids, the search for causative factors by means of patch tests can be carried on during such treatment. Corticosteroid therapy even though highly effective, is not indicated in chronic eczematous eruptions, except for cases with widespread and disfiguring lesions which do not respond to other measures or with itching so annoying as to interfere seriously with the patient's physical and mental well-being. Under no circumstances does the effective use of corticosteroids in these or other eruptions relieve the physician of his duty to search for and eliminate all causal or contributory factors.

Atopic Dermatitis Atopic dermatitis is another common dermatosis in which corticosteroid therapy is always highly effective, again provided that the dosage is adequate. Since the large majority of cases of atopic dermatitis can be very satisfactorily managed with other measures, corticosteriods are not indicated as routine systemic treatment, and should be reserved for exceptionally severe and extensive treatment-resistant cases. I am especially referring here to those patients who in former years were forced to undergo the dislocations entailed in making a complete environmental change. This includes also infants and young children with intractable widespread atopic infantile eczema. However both the physician and patient must be aware of the fact that corticosteroid treatment in such cases may have to be continued over a period of months and sometimes even years.

Instances have been reported where eczematous or eczematoid eruptions have recurred and were much worse after discontinuation of corticosteroid therapy than they had been before its inception. I have not encountered such cases with a rebound phenomenon attributable to an aggravating effect of corticosteroid therapy itself. Perhaps the eruption in the reported cases would have been worse even if no corticosteroid treatment had been given. Moreover it appears possible that the patients may have become allergic to other topical or systemic medicaments which were used concomitantly with the corticosteroid. In that event the allergic manifestations due to the other medicament may well have been suppressed during corticosteroid therapy but became clinically manifest after its discontinuation.

Pruritus Ani et Vulvae. Good results are often achieved with corticosteroids in pruritus ani and vulvae, but their use should be restricted to those exceptional cases which are unusually persistent, distressing, and resistant to other forms of treatment. It must be stressed once more that whenever corticosteroids are being administered to such patients, all measures must be taken simultaneously to eliminate the cause of the trouble, or if there is no specific cause to administer the best available form of treatment for the underlying dermatosis such as psoriasis or seborrheic dermatitis.

Urticaria. The results of systemic corticosteroid treatment in urticaria and angioneurotic edema in general have been somewhat disappointing. High doses often are required to obtain benefits, but even then the effects are irregular and unpredictable. Nevertheless, a trial with corticosteroid treatment is worthwhile when response to administration of vasoconstrictors, antihistamines, and other therapeutic agents is unsatisfactory and corticosteroid treatment is a must in cases of severe and dangerous angioneurotic edemas. In urticaria and angioneurotic edema prednisone is preferable to ACTH because ACTH itself has been known to cause urticaria and erythema multiforme-like drug reactions.

Psoriasis. The common variety of psoriasis on the extensors of the arms and legs, on the scalp and genitals, etc., usually responds to corticosteroids only in doses which are too high for prolonged administration save for the exceptional case. Such treatment therefore is not indicated in the management of cases of psoriasis vulgaris. Psoriatic exfoliative erythroderma, however responds excellently as do most cases of exfoliative dermatitis due to other causes, and in view of its serious nature psoriatic erythroderma is a definite indication for corticosteroid treatment.

Recent experience has shown that triamcinolone, a new analog of prednisolone, often produces much better results in psoriasis vulgaris than prednisone and other available analogs of cortisone. By using triamcinolone in relatively small to moderate doses, a very significant improvement has been obtained in cases of widespread psoriasis vulgaris. If further experience with triamcinolone or other compounds with similar or greater therapeutic efficacy do not reveal prohibitive side effects, it appears possible that systemic corticosteroid therapy in small to moderate doses may yet prove effective and practical for use in selected cases of psoriasis vulgaris, an advance which would fill one of the most important gaps in dermatologic treatment.

Lichen Planus. In acute and widespread lichen planus systemic corticosteroid treatment often appears to be very effective and is indicated for suppression of the eruption on a short-term basis. The conventional measures, however such as topical medication,

grenz or x radiation, and bismuth, still should be used for routine long-term management of lichen planus.

Herpes Zoster Alopecia Totalis. The pain of herpes zoster and particularly persistent postherpetic pain in elderly persons also are indications for a trial of systemic corticosteroid therapy In alopecia totalis and alopecia universalis corticosteroid therapy often causes partial regrowth of hair The number of cases, how ever which responds with complete regrowth or at least with a cosmetically useful result is very small. Perhaps combined sys temic and local injection therapy with corticosteroids will yield better results than either form of treatment alone. Postular psoriasis and acrodermatitis continua are among other dermatoses in which a trial with systemic corticosteroid therapy is warranted.

It is obvious that the decision as to whether systemic corticosteroid treatment is indicated in essentially benign dermatoses such as eczematous dermatitis, psoriasis, and lichen planus must be made for each case on the basis of the individual physician's best judgment.

Erythroderma, Pemphigus, Lupus Erythematosus. I shall now touch upon a group of serious very chronic, incapacitating or even fatal diseases in which corticosteroid treatment is indicated as a routine measure. Corticosteroid therapy is almost always effective in exfoliative erythroderma, pemphigus, and systemic acute and subacute lupus erythematosus provided that sufficient doses are given. Here one must stress the adequacy of dosage, since unless this point is kept in mind, patients who are in severe crises caused by these diseases may unnecessarily succumb. The routine starting dose in these serious diseases usually is at least 60 mg of prednisone. If there is no satisfactory improvement, this dose should be doubled at intervals of 1 to 2 days until there is evidence of a definite response. Once unmistakable signs of a pronounced response become evident, the dosage may be grad ually reduced until a maintenance dose has been established. Even after a satisfactory maintenance dose has been arri ed at, attempts should be made from time to time to ascertain whether an even lower maintenance dose can be used. In pemphigus for example as a *consequence of such repeated attempts at decrease*

in dosage, it has proved possible to maintain some cases on much smaller doses than appeared necessary at first, and in others treatment could be discontinued for more or less long periods. As a matter of fact, the advent of the corticosteroids has proved once more that the old saying "The eruption is not pemphigus unless the patient dies" is entirely false. We know now that some patients formerly probably died as a result of secondary factors such as infection or inanition rather than of the underlying cutaneous disease. Also in exfoliative erythrodermas, it has been possible in some cases to eventually discontinue the medication after many months or years of treatment. At other times, however, for example in pemphigus or lupus erythematosus, it has been necessary to raise the maintenance dose during periodic exacerbations. After every such flare-up and increase in dosage, it is desirable once more to attempt to reduce the maintenance dose to the required minimum.

In certain other serious generalized eruptions and dermatoses with systemic involvement, corticosteroid therapy unfortunately has proved to be of little value. In dermatomyositis, for instance, this treatment is only moderately and irregularly helpful. In generalized scleroderma the beneficial effects of corticosteroid therapy also are irregular and often so slight that they have been difficult to assess. Even so, one has had the impression in some patients that the progress of the disease was at least slowed up. No beneficial effects have been noted in acrosclerosis associated with scleroderma.

There are two infectious diseases in which sytemic corticosteroid therapy has been reported to have been used with a measure of success. In leprosy it is apparently possible to suppress some of the more severe acute manifestations such as lepra reactions. In syphilis Grupper and de Graciansky found that systemic corticosteroid therapy helps to suppress the Herxheimer reaction and accelerates the healing of the cutaneous lesions in patients under penicillin treatment. At this time it is not possible to say whether corticosteroid therapy eventually will be more widely used in these and perhaps certain other infectious diseases.

It is of the greatest practical importance that no such effect as

drug resistance appears to occur in long-term systemic corticosteroid therapy of benign or serious dermatoses. Not only is it not necessary to keep on increasing the dosage, but in some cases it is possible to gradually decrease the dose required for suppression of the dermatosis. Another salient fact which has emerged after years of experience is that there is no significant danger of unusual local or systemic infections during systemic corticosteroid therapy of skin diseases. This does not negate that exceedingly rare instances of such infections have been reported.

What about the future of corticosteroid therapy in dermatology? Obviously many interesting problems remain to be solved. The single most important problem, however is the continued search for a compound which exerts the beneficial cutaneous effects but lacks the objectionable side effects of the now available drugs. When such a compound will have been discovered, corticosteroid therapy will find vastly enlarged usefulness in the short and long-term management of acute and especially chronic benign dermatoses such as psoriasis.

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Morgan C Lindberg
and Victor D Newcomer

26

ANTIBIOTICS OTHER THAN PENICILLIN IN THE TREATMENT OF SYPHILIS

It is the purpose of this chapter to review the knowledge concerning the use of antibiotics other than penicillin for the treat ment of syphilis.

It should be stressed, however from the outset that penicillin is the currently accepted drug of choice for the treatment of all stages of syphilis. The *Treponema pallidum* is extremely sensitive to low concentrations of the drug and no resistant strains of this organism have been encountered to date [1]

Table 26-1 summarizes the dosage schedules currently recom mended by the Public Health Service [2a] and Thomas [2b] for the treatment of the various stages of syphilis with procaine penicillin G in oil with 2 percent aluminum monostearate (PAM) and benzathine penicillin G (Bicillin)

The major contraindication to the use of penicillin for the treatment of syphilis is the history of an untoward reaction result ing from a previous administration of the drug. There has been an increase in the frequency and severity of such reactions be cause of its widespread and repeated use [3] Antihistamines, intra enous procaine nonallergic penicillins, and more recently

Table 26-1 THE CURRENT TREATMENT OF SYPHILIS WITH PENICILLIN

Stage of syphilis	Benzathine penicillin G (Bicillin) units	Procaine penicillin G in oil with 2% aluminum monostearate (PAM) units
Primary and secondary	2,400 000 in single injection	Total, 4,800,000 1st injection, 2,400,000 2d injection, 1,200,000 3d injection, 1,200,000 Each given t 2 to 4-day intervals
Latent, early or late	Same as abov	
Late symptomatic (cardiovascular gummatous, osseous)	Total, 7,200,000 1st injection, 2,400,000 2d injection, 2,400,000 3d injection, 2,400,000 Given at 2 to -day intervals	Same as abov
Neurosyphilis		Total, 10,800 000 900,000 every 24 hours for 12 injections
Pregnancy	Same as the arious stages abov	
Congenital Early (less than 2 years)		Total, 1,500,000 150,000 every 24 hours for 10 injections
Late	Same as for comparable manifestations of acquired syphilis	

According to Thomas [2*b*].

tho corticosteroids have been employed in the attempt to prevent or abort such reactions [4] Although occasional successes have been reported [5] their use is of questionable value and inherently dangerous.

Recently penicillinase has been suggested for the treatment of undesirable side reactions developing from the administration of penicillin [6] but this substance does not appear to be of any value in the control of the more acute and serious types of untoward reactions.

Because of the difficulties and uncertainties encountered in evaluating the status of patients with such histories it appears wisest and most practical at the present time to employ a treponemocidal agent other than penicillin for the treatment of syphilis.

Since the introduction of penicillin in 1943 many other antibiotics have appeared in clinical practice. Most of these have been found to possess treponemocidal activity and therefore are potential substitutes for penicillin.

Penicillin therapy however has been so effective in reducing the over-all incidence of syphilis that it has become increasingly difficult to obtain enough clinical material to evaluate these drugs adequately in the treatment of the various stages of syphilis. Most clinical opinions are based on observations made in relatively small series of cases and over short periods of time. Additional information has been gained from in vitro studies and the treatment of experimental syphilis in rabbits. These latter studies have served as a rapid method of determining the treponemocidal potential of these newer antibiotics and have provided a method of comparing the effectiveness of several antibiotics under identical conditions, but they obviously cannot replace detailed clinical studies in man

A review of such experimental studies shows that none of the antibiotics in current use comes close to approaching the therapeutic efficacy of penicillin in the treatment of syphilis in rabbits [7] Hosoya et al. [8] however in an in vitro immobilization study which has not been confirmed to date, found a new antibiotic, trichomycin, to be 148 times higher in activity than penicillin.

Turner and Schaeffer [70] studied many of these antibiotics on a comparative basis in experimental syphilis in rabbits. Their purpose was to evaluate the possibility that the widespread use of these drugs in other diseases might have had an indirect impact on the treponemal diseases and also to obtain comparative data concerning the range of effectiveness of antibiotics other than penicillin on syphilis. They felt that their data permitted a rough approximation of comparative treponemocidal properties

of the various antibiotics tested. They listed them in the following order of effectiveness, with the most active listed first

1. Penicillin
2. *Carbomycin and erythromycin*
3. Oxytetracycline and chlortetracycline
4. Chloramphenicol and streptomycin

Kolmer [7b] similarly investigated the therapeutic effectiveness of 10 different antibiotic compounds in the treatment of acute syphilitic orchitis of rabbits. His results are summarized in Table 26-2.

TABLE 26-2 A COMPARISON OF THE APPROXIMATE MINIMAL CURATIVE DOSES OF 10 DIFFERENT ANTIBIOTIC COMPOUNDS IN RABBIT SYPHILIS

Antibiotic	Total dosage, mg/kg
Benzathine penicillin G	2
Oxytetracycline	50
Tetracycline	100
Chlortetracycline	200
Bacitracin	200
Erythromycin	200
Carbomycin	200
Streptomycin	500
Chloramphenicol	800
Polymyxin B	100 (no curative activity)

Adapted from Kolmer [7b].

We now pass to a review of the antisyphilitic value of the antibiotics in current use.

STREPTOMYCIN

Dunham and Rake [9] found that penicillin G was more than three thousand times as effective as streptomycin in experimentally produced syphilis in rabbits. Fisken and Gruhzit [10] observed no effect on the course of syphilis in rabbits in dosages as high as 10,000 units per kilogram per day for 13 days. Kolmer [11] was unable to obtain complete cures in acute syphilitic orchitis in rabbits given doses as high as 240,000 units per kilogram over a period of 8 days. Rake et al. [12] in another study

found streptomycin capable of curing rabbit syphilis, but only at relatively enormous dosages. They also found that penicillin and streptomycin in combination had no better than an additive effect.

No clinical studies were ever done because of these findings.

BACITRACIN

Bacitracin has been shown to be effective in the treatment of rabbit syphilis by Eagle and Fleishman [13*a* *b* *c*,] An intramuscular dose of 1,300 units per kilogram repeated once daily for 4 days cured approximately half of the animals tested. A striking synergism was noted in the therapeutic effect of penicillin and bacitracin in that as little as 1 mg per kilogram of penicillin (approximately one-fortieth of the CD_{50} dosage of penicillin alone) and 1,280 units per kilogram of bacitracin (approximately one-seventh of its CD_{50} value) were curative if used together

Although these data were reported because of their possible significance in the treatment of human syphilis, clinical studies have not been done in man, because *bacitracin is too toxic for* routine systemic administration.

TYROTHRICIN

Kolmer and Rule [14] found that the maximum single tolerated dose of tyrothricin for adult rabbits by intravenous injection was about 0.0008 gm per kilogram. Fifteen intravenous injections of 0.0001 gm per kilogram at daily intervals (totaling 0.0015 gm per kilogram) were completely ineffective in the treatment of acute testicular syphilis of rabbits. Also, the systemic toxicity of tyrothricin has limited its use in man to topical applications.

CHLORTETRACYCLINE

Wiggall et al. [15] found that Aureomycin given intramuscularly to rabbits in total doses of 50, 100 and 200 mg per kilogram produced a decrease of 50 to 90 per cent in the number of treponemata in cutaneous syphilomas in 48 hours. Complete heal

CD_{50}: That dose curing 50 per cent of infected animals.

ing of the lesions occurred in about ten days. They decided, however that in animals and man Aureomycin, in the dosages used and by the routes employed, was relatively slow in causing the disappearance of organisms from open lesions when compared with penicillin. Unpublished data of Nelson were cited to the point that in vitro Aureomycin has only one-thousandth the treponemal immobilizing effect of penicillin. They also noted that the use of Aureomycin in the treatment of other venereal diseases might mask the diagnosis of syphilis.

Chlortetracycline, because of its early introduction, has received more extensive use in the treatment of syphilis than most of the other antibiotics. In addition, patients so treated have been followed over a longer period of time. Table 26-3 summarizes these studies.

Rodriguez and his coworkers [16*a* *b* *c*] have published several reports on the efficacy of chlortetracycline in the treatment of early syphilis In their most recent report [16*c*] they presented their data obtained from the observation, over a period of from 12 to 15 months of 101 patients with dark field positive primary and secondary syphilis who were treated with chlortetracycline. They administered 2 gm immediately then 1 gm every 4 hours to a total dosage of 70 gm in 11¼ days. At the end of a 12 to 15 month period they obtained a seronegativity rate of 68.2 per cent. When satisfactory results were used as the yardstick of evaluation, they found no significant difference between the results obtained by administering 4,800,000 units of aqueous penicillin G in 60 intramuscular injections over a period of 7½ days (86 per cent) and those obtained with the chlortetracycline (76 7 per cent) They concluded that Aureomycin definitely had a therapeutic effect in early syphilis which was comparable to that of penicillin.

Chen et al [17] treated two patients with dark field positive primary syphilis with 250 mg four times a day for 2 weeks. The purpose of this study was to see if the 1 to 2 night doses previously adhered to could be omitted without impairment of the desired clinical response. From the results obtained in these two cases it appeared to them that Aureomycin was effective

against primary chancres when administered in the daytime hours only as the serological tests of both the patients were negative 4 and 5 months later respectively

Irgang and Alexander [18a, b] treated 68 Negro males with primary or secondary syphilis with chlortetracycline Various routes and total dosages were employed. The patients were followed up for a period of 12 months. At the end of this time they were given routine antisyphilitic therapy with penicillin and bismuth. There were no clinical failures in this series, and they concluded that Aureomycin had a definite value as an antisyphilitic drug. They suggested a dosage schedule of 2 gm orally (0.5 gm every 6 hours) and 50 mg intramuscularly (25 mg every 12 hours) daily for 3 weeks, both routes to be employed concurrently

Robinson and Robinson [19] treated dark field–positive early syphilis in 20 patients. Chlortetracycline was given orally to 10 patients in a dosage of 1 or 3 gm immediately followed by 0.5 gm every 4 hours for 15 days. In 10 similar patients, 100 or 200 mg of the drug was given intravenously daily for 15 days The surface spirochetes disappeared in 18 to 72 hours in those patients who received the drug orally and in both groups the lesions of early syphilis healed in 7 to 14 days. Reductions in the serologic titer were also observed. In a 2 to 4-year follow-up study [20] 6 of the 10 orally treated patients were available for evaluation. Of these, five patients had a negative reaction to serological test for syphilis, and the remaining patient had a weakly positive reaction to test (2 Kahn units) Seven of the ten patients treated intravenously were available for follow-up studies. Five were seronegative, one had a serological relapse, and one was still seropositive having a titer of 4 Kahn units. They concluded that chlortetracycline is of value as an antisyphilitic agent and could be used to replace penicillin if a necessity arose provided the patient could be kept under proper supervision

Crowe and Johnson [21] treated a patient with syphilitic osteoperiostitis, and with an incidental finding of central nervous system syphilis. The patient was given 0.75 gm of chlortetracycline orally four times daily to a total of 50 gm. Six months

Table 26-3 DOSAGE SCHEDULES AND REPORTED EFFICACY OF CHLORTETRACYCLINE IN TREATMENT OF SYPHILIS

Source	No. of patients treated	Type of disease	Dosage schedule	Total dose	Route	Follow-up period	Results
Rodriquez et al. [16]	101	Primary and secondary	2 gm stat., 1 gm q 4 h.	70 gm	PO	12–15 months	As good as with 4.8 m. units penicillin G.
Chen et al. [17]	9	Primary	0.25 gm q i.d.	50 gm	PO	5 months	Early healing. STS negative within 5 months.
Ingung and Alexander [18]	18	Primary and secondary	20 mg IM q 12 h. and 0.5 gm q 8 h PO	17–45 gm	PO and IM		Healing in less than 21 days. Dark-field negative in 24–72 hours. All but 4 to negative, STS
	24	Primary and secondary	20–50 mgm q 6–12 h.	0.34–1.8 gm	IM		Faster healing with 50 mg q 12 h. than with less, but dark-field negative within 48 hours and healing within 21 days.
	21	Primary and secondary	50 mg q 8 h.	2.8–4.4 gm	IV		Slower healing than with 50 mgm q 12 h. IM. Dark-field negative within 53 hours.

	5	Primary and secondary	500 mg q.12 h.	7.8 gm	IV		Dark-field negative in 48 hours, but lesions did not heal faster than with above therapy
Robinson and Robinson [19, 20]	10	Primary and secondary	1–3 gm stat. and 0 5 gm q 4 h.	43–47 gm	PO	2–4 years	6 followed 5 STS nega tive; the other positive to 2 Kahn units. Lesions healed in 7 14 days.
	10	Primary and secondary	0.1 or 0.2 gm daily	1.5–3 gm	IV	2–4 years	Lesions healed 7 14 days; of 7 followed, 5 STS negativ e, 1 serological relapse, 1 positive t 4 Kahn units.
Crow and Johnson [21]	1	Periostitis	0 75 gm q.i.d.	50 gm			Excellent ray results. Improvement in spinal fluid findings.
Kierland and O'Leary [23, 24]	21	Neurologic		50–90 5 gm	PO	1 year	Continued improvement in cerebrospinal serol ogy except one
Taggart t l. [25]	128	All	30-120 mg. kg/day	8 4–18.6 gm	PO	12–15 months	Almost all to negati STS. Felt that 00 mg/kg/day for 8 days wa comparable t penicil lin therapy

after completion of therapy the areas previously involved showed distinct improvement. Roentgenologic studies demonstrated a reduction in the periosteal thickening, a general smoothing off of the periosteal shadow and a filling in of the areas of rarefaction. There was also considerable improvement in the cerebrospinal fluid findings. They concluded that the excellent results clinically, roentgenologically and serologically warrant further use of this antibiotic in syphilis.

With the early knowledge [22*a* *b* *c*] that chlortetracycline administered by mouth produced rapid healing of the cutaneous lesions of early and late syphilis Kierland and O'Leary [23] treated 12 patients with various types of neurosyphilis. They used a total oral dosage which varied from 50 to 90.5 gm. In all but one there was satisfactory and rapid clinical improvement. There was also a rapid improvement in the findings in the cerebrospinal fluid, particularly in the cell count and in the protein value. They concluded that the results with Aureomycin were equivalent to those obtained with penicillin. They felt that Aureomycin by mouth was indicated for those patients with neurosyphilis who have a resistance or hypersensitivity to penicillin. In a subsequent progress report [24] they again reviewed the status of 10 of the 12 previously treated patients and reported on 9 additional neurosyphilitic patients. Again they found that Aureomycin produced long-standing benefit and that Aureomycin was equal to penicillin in the treatment of neurosyphilis. They suggested approximately 60 gm of Aureomycin (2 to 4 gm given daily in divided doses) as a single or first course of therapy.

Taggart et al. [25] have summarized their 12 to 15 month posttreatment observations of 128 patients. Several dosage schedules were used. They concluded that the results obtained in the various stages of syphilis following the administration of 60 mg per kilogram per day for 8 days were comparable to those following the use of intramuscular penicillin over a comparable period of time. They also conclude that Aureomycin could be used for the treatment of syphilitic patients for whom oral administration was to be preferred or in the treatment of patients with syphilis who were allergic to penicillin.

Thirteen pregnant women were included in this series· the results in twelve were quite satisfactory

CHLORAMPHENICOL

Early studies directed toward evaluating the antitreponemal properties of chloramphenicol in rabbit syphilis proved disappointing. Smith et al. [26] found no change in the lesions and no disappearance of treponemata in rabbits infected with the Nichols strain of *Treponema pallidum* after they had been given 25 mg per kilogram per day of Chloromycetin intramuscularly in two divided doses for a period of 8 days. Daily dosages of 50 and 100 mg per kilogram temporarily cleared the lesions of treponemata.

Robinson et al. [27] found chloramphenicol in concentrations of 100 μg per milliliter to have no immobilizing effect on the treponemata in vitro at 24 or 48 hours. The failure of the drug to inhibit the motility of virulent spirochetes suggested to them that chloramphenicol was not directly treponemicidal in the dosages used but rather that any effect on early clinical syphilis was due to inhibition of reproduction by the organism.

In comparing treponemicidal properties of various antibiotics in rabbit syphilis, both Turner [7*a*] and Kolmer [7*b*] rated chloramphenicol as relatively ineffective Gruhzit and Fisken [28] explained the comparatively large amounts of chloramphenicol needed to treat syphilis successfully in rabbits by the fact that chloramphenicol rapidly disappears from the blood stream of rabbits and high serum concentrations are difficult to maintain. This is in contrast to the relatively high and prolonged concentrations of chloramphenicol obtainable in the blood stream of man.

Smadel et al. [29] in a preliminary report on the use of chloramphenicol in the treatment of acute gonorrheal urethritis, observed the effect of the administration of this drug on the disappearance of treponemata in the chancres of concomitant early syphilis in two of their patients.

In one patient, 4 gm in a single dose had no effect on the treponemata during the next 18 hours. When 3 gm was then given

and this followed by 0.5 gm every 3 hours for a total of five doses, treponemata were not observed, and the chancre slowly healed over the succeeding week. The second patient was given an initial dose of 70 mg per kilogram of body weight and an additional 58 mg per kilogram over the next 15 hours. Seventeen hours after treatment was started, motile treponemata could no longer be found, but there was no evidence of healing during the succeeding 3 days.

Robinson et al. [19] treated 14 patients who had dark-field–positive lesions with chloramphenicol. In 8 of them (71.4 per cent) the dark field became negative in 24 hours, and the remainder became negative in 48 to 72 hours. Ten of these patients completed a preliminary 6 months follow-up period, and of these seven (70 per cent) had become seronegative and had negative spinal fluid examinations. Two others showed a drop in serologic titer from 64 to 4 units. Two pregnant women were treated, and both delivered normal nonsyphilitic infants. An initial dosage of 3 gm was given, and this was followed by 0.5 gm every 4 hours to a total of 48 gm over a 15-day period. Two to four years later only 30 per cent had become and remained seronegative.

They concluded that Chloromycetin, Terramycin, and Aureomycin administered either orally or intravenously were of value as antisyphilitic agents but that they should replace penicillin only if a necessity arose, and if the patient could be kept under supervision.

Taggart and his coworkers have presented their findings and opinions in a series of articles [30*a–d*]. Their last publication [25*b*] summarized the results of therapy in 104 patients predominantly with early syphilis who had been observed for periods of 12 to 15 months. They concluded that the results of treatment with chloramphenicol in a dose of 60 mg per kilogram per day for 6 to 8 days indicated that the per cent reaching seronegativity and the cumulative per cent retreated were comparable to those results which have been reported following the use of 300 000 units or more of penicillin per day for 7½ to 10 days. They believed that Aureomycin and Chloromycetin could be used for the treatment of syphilitic patients in whom oral administration was to be pre-

ferred to parenteral use, or in those patients allergic to penicillin. In a small series, they found that Aureomycin treatment in preg nancy appeared to give more favorable results than Chloromycetin but felt that greater experience needed to be gained before definite conclusions could be made.

The healing mechanism in ulcerative gummas appeared to be different with chloramphenicol than with penicillin. The latter produces initial healing at the periphery of such a lesion. Healing under Chloromycetin therapy seems to be initiated from the base of the lesion until the skin level is reached, then very rapid epithelialization occurs across the surface.

They advised that Chloromycetin be given for at least 15 days for the treatment of neurosyphilis.

Chloramphenicol was used intramuscularly by Olansky et al. [31] in the treatment of 63 patients with early syphilis. They were given 2 gm every 12 hours for 6 days, a total of 24 gm, or 2 gm daily for 6 days, a total of 12 gm. Follow-up period ranged from 3 to 13 months. Results which were considered satisfactory oc curred in all cases, and the 24-gm dosage schedule did not appear to be superior to the 12-gm dosage schedule They felt, however that further studies were in order to work out optimal time-dose relationships and possible outpatient therapeutic schedules.

Mazzini and Blasi [32] on the basis of treating 10 patients having early syphilis with Chloromycetin, given orally suggested a high daily dose of 100 per kilogram of body weight, for 6 to 8 days.

Table 26-4 summarizes these clinical studies.

OXYTETRACYCLINE

Clinical studies with oxytetracycline are summarized in Table 26-5.

Hendricks et al. [33] treated six patients with early syphilis. They were given 60 mg per kilogram of body weight per day for 8 days. Clinical healing of lesions occurred promptly and no organisms were observed.

Robinson and Robinson [19, 20 34] treated five cases of dark field–positi e early syphilis with 3 gm immediately followed by

Table 26-4 CLINICAL STUDIES OF DOSAGE SCHEDULES AND EFFICACY OF CHLORAMPHENICOL IN TREATMENT OF SYPHILIS

Source	N of patients treated	Type of disease	Dosage schedule	Total dose	Route	Follow p period	Results
Smadel t al. [99]	1	Early	4 gm, then 3 gm, then 0 5 gm q 3h for 5 doses	9½ gm	PO		N effect with first dose Healed slowly Dark field-negative 1 week.
	1	Early	0 mg kg stat and 58 mg kg over 15 h period	9 gm	PO		Dark field-negati e 17 hours. No healing 1 3 days.
Robinson and Robinson [19]	14	Early	3 gm stat. 0.5 gm q 4l	48 gm	PO	6 months	Dark-field-negative in 48–72 hours (in 24 hours in 8) Seven of 10 seronegati e in 6 months. Two others had drop in titer from 64 to 4.

T gart et al. [30]	79	Early	30–120 mg/kg/d	8.4–50.4 gm	PO	12–15 months	All favorable. Those with 60-mg dose or more did best.
	11	Early latent	30–120 mg/kg/d	8.4–50.4 gm	PO	12–15 months	STS decreased, but no negatives.
	8	Late	60 mg/kg/d	63 gm			Lesions healed, recurred in one
	5	CNS	60 mg/kg/d	63 gm	PO	12–15 months	Essentially negative results, but cell counts on CSF decreased.
Olansky et al. [31]	7	Primary	2 gm q.12 h.	24 gm	IM	3–13 months	15 became seronegative. 4 showed satisfactory decline.
	13	Primary	1 gm q.12 h.	12 gm	IM	3–13 months	
	43	Secondary	1 gm q.12 h.	12–24 gm	IM	3–13 months	[illegible]8 became seronegative. 15 showed satisfactory decline.
Ma[illegible] and Bl[illegible] [32]	9	Early	40–65 mg/kg/d	48–60 gm	PO	7 months	Slow healing of lesions.
	6	Early	0–100 mg/kg/d	32–126 gm	PO	7 months	Rapid healing.

Table 26-5 CLINICAL STUDIES OF DOSAGE SCHEDULES AND EFFICACY OF OXYTETRACYCLINE IN TREATMENT OF SYPHILIS

Source	No. of patient treated	Type of disease	Dosage schedule	Total dose	Rout	Follow-up period	Results
Hendricks et al. [33]	6	Early	60 mg kg d.	32 gm	PO	1 month	Lesion healed promptly STS' became negative.
Robinson and Robinson [34]	5	Early	3 gm stat., 80 5 gm q 4 h.	48 gm	PO	2–4 years	Of 4 followed: 3 had negative STS 1 had a relapse.
Ingang and Alexander [36]	10	Early	0.5 gm q.6 h.	28 gm	PO	3 months	Most lesions healed fairly quickly. One was resistant. STS's of 5 followed became negative.
Dunlop and Robinson [38]	4	Early	0.5 gm/d.	5 gm	IV	3–7 months	Slow healing—8–20 days. Fair STS results. Do not advise this method of treatment.
Baker [39]	16	Early	0.2 gm b.i.d.	4 gm	IM	6–18 months	Successful in 12; 4 failures.

0.5 gm every 4 hours for 15 days. The lesions became dark-field-negative in 24 to 32 hours In a 2 to 4 year follow-up study [21] one patient was lost, three became seronegative, and in one there was a serologic relapse. They concluded that Terramycin was of definite value as an antisyphilitic agent but should replace penicillin only if a necessity arises. Robinson [35] felt that oxytetra cycline *was the drug of choice for the treatment of syphilis in* those patients intolerant to penicillin. He advocated a total dosage of 48 gm over a 15-day period for early syphilis and 90 gm over a period of 30 days for benign late syphilis, cardiovascular syphilis, and central nervous system syphilis.

Irgang and Alexander [36] treated 10 cases with early acquired syphilis. The patients were followed for a period of 12 weeks. Their early results indicated that oxytetracycline was of value in the treatment of syphilis. A dosage in excess of 2 gm per day was recommended. Moreover treatment should be continued for at least 2 weeks. It was also suggested that Terramycin might be used conjointly with bismuth subsalicylate therapy This latter statement was based on work done by Kolmer in the treatment of experimental syphilis of rabbits [37] He found that intravenously injected Mapharsen and intramuscularly injected bismuth salicylate yielded pronounced synergistic or additive therapeutic effects when given along with orally or intramuscularly administered oxytetracycline

Dunlop and Robinson [38] treated four patients with early syphilis with 0.5 gm of oxytetracycline daily for 10 days. This was given intravenously in 250 ml of sterile distilled water In the dosage used, Terramycin was not as effective as infinitesmal (150 units per kg) doses of crystalline penicillin G in eliminating surface treponemata. They concluded that further use of intravenous Terramycin for the treatment of syphilis did not appear justified in view of the difficulty of administration and the proved efficacy of other forms of treatment.

Baier [39] treated 16 patients with early syphilis with oxytetra cycline intramuscularly Two hundred milligrams twice daily for 10 days were given to a total dose of 4 gm. Twelve had successful responses and four were considered failures when evaluated 8 to

16 months later The intramuscular administration of oxytetracycline was considered to be of definite value in the treatment of early syphilis, but a total dose of 6 to 8 gm was recommended.

ERYTHROMYCIN

Keller and Morton [40] found that cultivatable treponemata are very susceptible to the action of erythromycin and suggested in vivo and clinical studies to ascertain the efficacy of this antibiotic Turner and Schaeffer [7a] and more recently Kolmer [7b] found erythromycin to be effective in experimental rabbit syphilis.

Alexander and Schoch [41] have treated four patients with syphilis—one with seropositive primary and three with secondary syphilis. All were given 200 mg of erythromycin four times a day for 8 days. Dark field examination showed negative lesions within 24 hours in three patients and at 30 hours in the fourth patient. The lesions healed as promptly as with other therapeutic agents. They concluded that the drug was effective in early syphilis because of the early disappearance of *T pallidum* from the lesions, the rapid healing of the lesions, and the reduction of the serologic titer in each of the patients who were observed 3 weeks to 5½ months later (See Table 26-6.)

TETRACYCLINE

Kolmer [7b] has shown tetracycline to be effective in the treatment of experimental syphilis in rabbits. The report by Rajam et al [42] constitutes the only clinical study concerning the use of this antibiotic. They have treated three cases with 500 mg every 6 hours for 12 days. Two of these were pregnant females with dark field–positive lesions. The lesions became negative after 120 hours, and healthy babies were delivered at term. The titer of one fell from 64 to 2 units. One week was required for the disappearance of the treponemata from a third female with dark field–positive secondary lesions. Her serology was negative at 6 months. In addition, one ten-year-old child with early syphilis was given 250 mg every 6 hours for 24 days. The lesions healed in 12 days, and the serologic test for syphilis declined from 128 units to 16 units within 2 months. (See Table 26-6.)

Table 24-4 CLINICAL STUDIES OF DOSAGE SCHEDULES AND EFFICACY OF ERYTHROMYCIN, TETRACYCLINE, AND CARBOMYCIN

Source	No. of patients treated	Type of disease	Dosage schedule	Total dose	Rout	Follow-up period	Results
			ERYTHROMYCIN				
Alexander and Schoch [41]	4	Early	0.2 gm q i.d.	6.4 gm	PO	3–24 weeks	Dark-field-negative in 30 hours. Lesions healed promptly. STS negative within 24 weeks.
			TETRACYCLINE				
Rajam et al. [42]	2	Early pregnant	0.5 gm q 6 h.	24 gm	PO		Dark-field-negative in 120 hours. Normal deliveries. STS to doubtful.
	1	Secondary	0.5 gm q 6 h.	24 gm	PO	6 months	STS became negati e.
	1	Early	0.25 gm q 6 h.	24 gm	PO	2 months	STS titer declined from 128 to 16.
			CARBOMYCIN				
Buckingam et al. [43] Hookings and Gra er [44]	16	Primary	1 gm stat., 0.5 gm q.i.d.	21 gm	PO	2–23 months	Most lesions healed in 14 days. All STS negatr in 5-6 months.
	22	Secondary	1 gm stat., 0.5 gm q i.d.	21 gm	PO	2–23 months	STS titer decreased i all, most became negative.
	3	Tertiary	1 gm stat., 0.5 gm q.i.d.	43 gm	PO	2–23 months	STS declined. Gummas healed.

CARBOMYCIN

Turner and Schaeffer [7a] *found carbomycin to be effective in* experimental syphilis in rabbits. Kolmer [7b] substantiated this finding. Buckinger et al. [43] administered carbomycin to 11 patients with dark field–positive early syphilis. Various dosage schedules were used. An oral dose of carbomycin of 2 or 3 gm a day was effective in bringing about the disappearance of treponemata from lesions in 36 to 72 hours. Hookings and Graves [44] from the same clinic later reported on a larger series. This included 16 patients with primary syphilis, 22 patients with secondary syphilis, and 3 patients with other stages of the disease. An initial dose of 1 gm was used and this was followed by a daily dose of 2 gm given as 500 mg four times daily to a total of 21 gm in the early syphilis and 42 gm in the others.

Their longest period of follow-up was 23 months, and the shortest was two months. The chancres of all the patients with primary *syphilis became dark-field–negative and the serologic tests for* syphilis in these cases reverted to negativity within 6 months. The chancres in the majority of instances healed within 14 days following therapy. There was also a good therapeutic result in those patients with secondary syphilis. In all cases there was a reduction of the serologic titer during the period of follow-up the majority becoming negative. The titer declined in one case of early latent syphilis. Complete healing of lesions occurred in two cases of tertiary syphilis with gummatous lesions of the skin.

They concluded that carbomycin is effective as a treponemocidal agent. It rapidly renders dark-field–positive syphilitic lesions negative. It will reduce the titer of the VDRL reaction, and will heal gummmatous lesions of the skin. (See Table 26-6.)

NOVOBIOCIN

Garson and McLeod [45] have recently published their preliminary results on the effect of novobiocin in experimental syphilis in rabbits. When novobiocin was administered in Upjohn diluent USA for 14 days, rabbits given daily doses of 120, 60, or 30 mg per kilogram became asymptomatic by the end of the treatment

period. All the animals survived, and no relapses occurred during a period of 5 weeks. No clinical studies are available.

SYNNEMATIN B

Wheeler et al. [46] have treated one patient with primary syphilis with synnematin B He was given 1,000,000 units intra muscularly and then 40,000 units three times a day for 8 days. The primary lesions became negative in 24 hours, and 10 days later the positive reaction to Kahn test had decreased from 128 units to 64 units. The patient s chancre was well healed 17 days later and the Kahn was positive in only 32 units. Two months later the reaction to Kahn test was doubtful, and at 7 months it became negative.

DISCUSSION AND CONCLUSIONS

It is becoming increasingly apparent that a wide variety of effective antibiotics are currenty available for the treatment of syphilis. None of these has received extensive and detailed studies in respect to their antisyphilitic value, and a great deal more experience must be gained before optimal dosage and relative values can be determined. The undertaking of such studies has become increasingly difficult because of a dwindling reservoir of clinical material. From the data available to date, however none of these antibiotics has been demonstrated to be more effective than penicillin, and this latter drug remains the treatment of choice for all stages of syphilis.

Table 26-7 MAXIMUM DOSAGE SCHEDULES OF VARIOUS ANTIBIOTICS FOR THE VARIOUS STAGES OF SYPHILIS

Drug	Dosage suggested	Stage of syphilis
Chlortetracycline	4 gm/d. 14d.	All
Oxytetracycline	4 gm d. 14d.	All
Tetracycline	4 gm d. 14d.	All
Chloramphenicol	4 gm d. 14d.	All
Carbomycin	2 gm d. 10½d.	Primary and secondary
Erythromycin	500 mg q.i.d. 8d.	Primary and secondary

Single reports, not confirmed.

The use of these antibiotics is indicated, however in those instances where penicillin is contraindicated. Instances also arise when it is desirable to evaluate the antisyphilitic effect of these antibiotics when they are being given for another disease and a syphilitic infection is found to be present also

Table 26-7 represents a summary of maximum dosage schedules for the various stages of syphilis. It must be stressed that patients so treated must be adequately followed.

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